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Docket No. MDAN/0003

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UNITED STATES PATENT APPLICATION FOR:

**EFFECTORS OF LYSOPHOSPHATIDIC ACID (LPA) SIGNALING AND THE USE
THEREOF**


INVENTORS:

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ATTORNEY DOCKET NUMBER: MDAN/0003

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Date of signature 2/20/04

EFFECTORS OF LYSOPHOSPHATIDIC ACID (LPA) SIGNALING AND THE USE THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] Embodiments of this invention generally relate to therapeutically effective compositions of matter and their uses. Specifically, embodiments of the invention relate to compositions containing effectors for lysophosphatidic acid (LPA) signaling and analogs and derivatives thereof, as well as methods of using these compositions.

Description of the Related Art

[0002] Phospholipids, such as phosphatidic acid (PA), phosphatidylinositol (PI), lysophosphatidic acid (LPA), lysophosphatidylinositol (LPI), lysophosphatidylcholine (LPC), are generally found to be involved in a broad range of biological processes and cellular events in a variety of plants and animals. Lysophosphatidic acid (LPA) has been reported to induce cell proliferation, differentiation, mitogenesis, wound healing, platelet aggregation and smooth muscle contraction, to prevent apoptosis induced by stress or stimuli during angiogenesis, to induce growth-factor-like responses and stimulate cell morphologic changes, cell adhesion, and cell migration, and to be used as an anti-wrinkle agent. More specifically, LPA has been reported to induce the production of T cell growth factor, e.g., interleukin 2 (IL-2), and to stimulate cell proliferation in serum free medium or in synergy with low concentration of fetal bovine serum. LPA has also been reported to induce a transient increase in cytosolic free calcium (Ca^{2+}) in many cell lines.

[0003] LPA is typically produced either extracellularly or intracellularly in response to various growth factors, including LPA itself, phorbol esters, epidermal growth factor and other factors. Further, the recent discovery of the LPA biosynthesis pathway has elucidated how LPA is produced in extracellular milieu. It is now known that LPA is generated sequentially from phosphatidylcholine (PC) by phospholipase A (PLA) into lysophosphatidylcholine (LPC), and from LPC into LPA

by an enzyme, ATX/lysoPLD ectophosphodiesterase, which has been implicated in cell motility and tumor invasion, neovascularization, and metastasis.

[0004] It is also known that LPA induces invasion *in vitro* and could play a role in the pathophysiology of cancers. Ovarian cancer-activating factor (OCAF) from ascites of ovarian cancer patients was purified, characterized and then identified as a mixture of multiple forms of LPA. The OCAF is responsible for the major activity of the ovarian cancer ascites to activate ovarian cancer cells. In addition, aberrant LPA receptor expression, LPA production, and/or expression of the enzymes for LPA synthesis are significantly increased in malignant cancer cell effusions and in multiple cancer cell lineages. It has been observed that activities of LPA in cancer lead to an increase in proliferation under anchorage-dependent and anchorage-independent conditions; prevention in apoptosis and anoikis; an increase in invasiveness; an inducement to cytoskeletal reorganization and change of cell shape; a decrease in sensitivity to chemotherapy agents; an increase in production of various regulators of neovascularisation and/or the mRNA expression of these growth factors or regulators/mediators, e.g., vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), IL-6, proteases (urokinase plasminogen activator (uPA), and/or LPA itself; and an increase in the activity of cancer development related proteases, e.g., matrix metalloproteinase 2 (MMP-2) and MMP-9. The results underscore the importance of LPA in cancer.

[0005] LPA signals by binding to specific receptors which, in turn, lead to specific targeted cellular events. LPA specific receptors belong to the membrane G protein coupled receptors (GPCR) protein family, whose structures span seven-times across cell membrane. Four mammalian LPA specific receptors have been identified so far, LPA1, LPA2, LPA3 and LPA4. They were formerly called endothelial differentiation genes (EDG), EDG2, EDG4, EDG7, and GPR23/P2Y9, respectively. LPA1 is the most widely expressed receptor, whereas LPA2 and LPA3 are aberrantly expressed in different cancer cells. LPA4 seems to be expressed at very low levels. In ovarian cancer, LPA2 and LPA3 appear to be positive stimulators and LPA1 appears to be a negative regulator that decreases cellular proliferation and

increases apoptosis and anoikis. These findings have suggested a role for LPA and LPA receptors as cancer markers for ovarian cancer screening.

[0006] In the case of prostate cancers, both LPA sensitive and LPA insensitive cell lines have been found. In some prostate cancer cell lines, LPA acts an autocrine growth factor. However, little is known about the biological functions of LPA and LPA receptors in prostate cancer. For most prostate cancers, androgen withdrawal provides the first-line of therapy, and under the selective pressure of hormonal ablation therapy, androgen-independent clones invariably arise, resulting in tumor progression and inevitable death. Androgen-insensitive prostate cancer cells are characterized by a low proliferative rate that decreases the efficacy of most chemotherapeutic regimens. In particular, LPA has been found to have potent growth and survival promoting activity for prostate cancer cells. For example, it was discovered that the LPA3 receptor can mediate cell growth and survival in human ovarian and prostate cancer cell lines using a LPA selective positive effector, an agonist 1-acyl-sn2-O-methyl-rac-glycero-3-phosphothionate (OMPT). It was also discovered that the LPA2 receptor can mediate cell migration in androgen-insensitive prostate cancer cells.

[0007] Thus, there remains a need for a method of controlling the function of LPA and/or LPA receptors with respect to cancer cell growth and survival. In addition, LPA plays a role in the pathophysiology of multiple other diseases, including atherosclerosis, hypertension, ischemia perfusion injury, diabetes, cardiovascular disease, stroke, prevention of toxicity of chemotherapy and radiation therapy, immunological function and others. Thus, modulators of LPA function may find utility in multiple diseases.

SUMMARY OF THE INVENTION

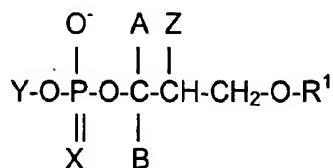
[0008] Embodiments of the invention generally relate to compounds and pharmaceutical compositions involved in LPA signaling and methods of treating a disease, such as cancer diseases, using compounds and compositions of the invention.

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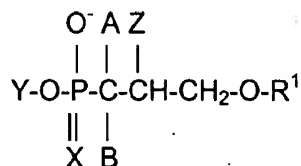
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[0009] In one embodiment, the invention provides a compound having the formula:



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, A is selected from the group consisting of hydrogen, hydroxyl, and halogen, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, Z is selected from the group consisting of hydrogen, hydroxyl, halogen, haloalkyl, haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, and alkynyloxy, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of hydrogen, halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof, and when X is oxygen and A and B are both hydrogen, then Y is not hydrogen.

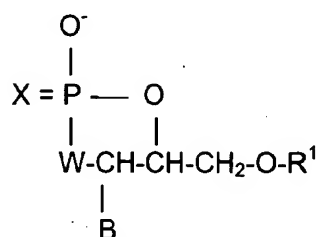
[0010] In another embodiment, the invention provides a compound having the formula:



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl,

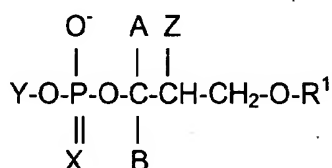
heteroaryloxy, aralkyl, aralkyloxy, A is selected from the group consisting of hydrogen, hydroxyl, and halogen, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, Z is selected from the group consisting of hydrogen, hydroxyl, halogen, haloakyl, haloalkyloxy, alkyl, alkenyl, alkylnyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, and alkynyloxy, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of halogen, saturated and unsaturated haloakyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkylnyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof.

[0011] In another embodiment, the invention further provides a compound having the formula:

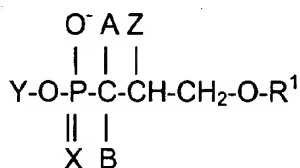


wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkylnyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, W is oxygen or a bond, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of halogen, saturated and unsaturated haloakyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkylnyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof.

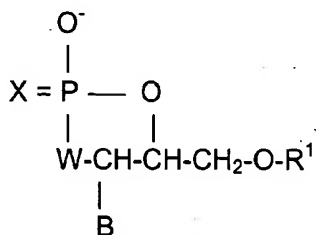
[0012] In yet another embodiment, the invention provides a pharmaceutical composition for treating a disease. The pharmaceutical composition includes a therapeutically effective amount of a compound having the formula:



or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof. In another embodiment, the pharmaceutical composition includes a therapeutically effective amount of a compound having the formula:

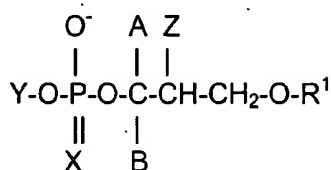


or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof. In still another embodiment, the pharmaceutical composition includes a therapeutically effective amount of a compound having the formula:

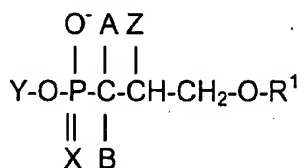


or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof.

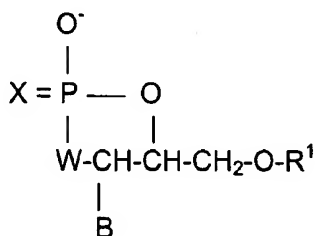
[0013] In yet another embodiment, the invention further provides a method for treating a disease, including administering a pharmaceutically effective amount of a therapeutically effective amount of a compound having the formula:



or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof. In another embodiment, the method includes administering a pharmaceutically effective amount of a therapeutically effective amount of a compound having the formula:



or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof. In still another embodiment, the method includes administering a pharmaceutically effective amount of a therapeutically effective amount of a compound having the formula:



or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof

[0014] In yet another embodiment, the invention provides a method for treating an androgen insensitive prostate cancer, including administering a pharmaceutically effective amount of a compound of a LPA derivative to a subject.

[0015] In yet another embodiment, the invention further provides a method for treating a cancer disease. The method includes administering a pharmaceutically

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effective amount of a LPA derivative to bind to a specific subtype of LPA receptor and inhibit cell growth.

[0016] The compound and/or LPA derivative of the invention includes 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

[0017] In addition, the compound and/or LPA derivative of the invention includes 2-alkyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-acyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-acyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

[0018] Further, the compound and/or LPA derivative of the invention includes 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, and derivatives thereof.

[0019] Still further, the compound and/or LPA derivative of the invention includes 1-lauroyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-myristoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-palmitoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-stearoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-oleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-linoleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-linolenoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-eleosteryl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate and derivatives thereof.

[0020] Additionally, the compound and/or LPA derivative of the invention includes 1-acyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-lauroyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-palmitoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-eleosteryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], and derivatives thereof.

[0021] Furthermore, the compound and/or LPA derivative of the invention includes 1-alkyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-lauryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-palmityl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-eleosteryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], and derivatives thereof.

[0022] Also, the compound and/or LPA derivative of the invention further includes 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-acyl-

sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-phosphonate, and derivatives thereof.

[0023] Still further, the compound and/or LPA derivative of the invention includes 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphonate, and derivatives thereof.

[0024] Still further, the compound and/or LPA derivative of the invention includes 1-alkyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, and derivatives thereof.

[0025] The compound and/or LPA derivative of the invention further includes 1-alkyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-acyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

[0026] Further, the compound and/or LPA derivative of the invention includes 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-

sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] So that the manner in which the above recited features of the present invention can be understood in detail, a more particular description of the invention, briefly summarized above, may be had by reference to embodiments, some of which are illustrated in the appended drawings. It is to be noted, however, that the appended drawings illustrate only typical embodiments of this invention and are therefore not to be considered limiting of its scope, for the invention may admit to other equally effective embodiments.

[0028] Figure 1 illustrates the chemical structures of LPAs.

[0029] Figure 2A illustrates the chemical structure of DPIEL.

[0030] Figure 2B illustrates the chemical structure of LPA derivatives, LPGs.

[0031] Figure 3 demonstrates the effect of OMPT-induced and 18:1 LPA-induced calcium mobilization in ovarian cancer cells (OVCAR3) and colon cancer cells (HT29).

[0032] Figure 4 demonstrates the concentration-response curves of OMPT and 18:1 LPA on calcium mobilization in OVCAR3 and HT 29 cells.

[0033] Figure 5 demonstrates the effect of DPIEL on OMPT-induced calcium mobilization in ovarian cancer cells (OVCAR3).

[0034] Figure 6 demonstrates the effect of DPIEL on 18:1 LPA-induced calcium mobilization in colon cancer cells (HT29).

[0035] Figure 7 demonstrates the effect of DPIEL on 18:1 LPA-induced calcium mobilization in androgen insensitive prostate cancer cells (PC-3).

[0036] Figure 8 shows that DPIEL inhibit phosphorylation of ERK activated by 18:1 LPA in androgen insensitive prostate cancer cells (PC-3).

[0037] Figure 9 illustrates chemical structures of various LPGs and their derivatives.

[0038] Figure 10 shows the mRNA expression levels of various LPA receptors in different cancer cells.

[0039] Figure 11 is a graph showing inhibition of calcium mobilization of 14:0 LPA by 14:0 LPG in DU145 cancer cells.

[0040] Figure 12 demonstrates inhibition of 14:0 LPA signaling by 14:0 LPG in DU145 cancer cell.

[0041] Figure 13 demonstrates the normalized response of the inhibition of 14:0 LPA signaling by 14:0 LPG in DU145 cancer cells.

[0042] Figure 14 is a graph showing 18:1 LPA-induced calcium mobilization in DU145 cancer cells.

[0043] Figure 15 is a graph showing 18:1 LPA-induced calcium mobilization in the presence of 10 μ M 18:1-acyl-LPG in DU145 cancer cells.

[0044] Figure 16 is a graph showing 18:1 LPA-induced calcium mobilization in the presence of 30 μ M 18:1-acyl-LPG in DU145 cancer cells.

[0045] Figure 17 demonstrates concentration-dependent inhibition of 18:1 LPA signaling by 18:1-acyl-LPG in DU145 cancer cells.

[0046] Figure 18 demonstrates normalized response of the inhibition of 18:1 LPA signaling by 18:1-acyl-LPG in DU145 cancer cells.

[0047] Figure 19 demonstrates the effect of 14:0 LPG and 18:1-acyl-LPG on OMPT-induced calcium mobilization in androgen insensitive prostate cancer PC-3 cells.

[0048] Figure 20 demonstrates the normalized response of the inhibition of 14:0 LPG and 18:1-acyl-LPG on OMPT-induced calcium mobilization in androgen insensitive prostate cancer PC-3 cells.

[0049] Figure 21 demonstrates the effect of 14:0 LPG, 18:0 LPG, and 18:1-acyl-LPG on 18:1 LPA-induced calcium mobilization in colon cancer HT29 cells.

[0050] Figure 22 demonstrates normalized response of the inhibition of 14:0 LPG, 18:0 LPG, and 18:1-acyl-LPG on 18:1 LPA -induced calcium mobilization in colon cancer HT29 cells.

[0051] Figure 23 demonstrates LPA2 receptor mediated lamellipodia formation for colon cancer HT29 cells in serum-free medium control.

[0052] Figure 24 demonstrates the effect of 10 μ M 18:0-acyl-LPG on serum-starvation mediated lamellipodia formation in colon cancer HT29 cells.

[0053] Figure 25 demonstrates the effect of 30 μ M 18:0-acyl-LPG on serum-starvation mediated lamellipodia formation in colon cancer HT29 cells.

[0054] Figure 26 demonstrates that 14:0 LPA induces LPA2 receptor mediated lamellipodia formation for colon cancer HT29 cells.

[0055] Figure 27 demonstrates the inhibition of 14:0 LPA-induced LPA2 receptor mediated lamellipodia formation by 10 μ M 18:0-acyl-LPG in colon cancer HT29 cells.

[0056] Figure 28 demonstrates the inhibition of 14:0 LPA-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 18:0-acyl-LPG in colon cancer HT29 cells.

[0057] Figure 29 demonstrates that 1% fetal bovine serum (FBS) induces LPA2 receptor mediated lamellipodia formation in colon cancer HT29 cells.

[0058] Figure 30 demonstrates the inhibition of 1% FBS-induced LPA2 receptor mediated lamellipodia formation by 10 μ M 18:0-acyl-LPG in colon cancer HT29 cells.

[0059] Figure 31 demonstrates the inhibition of 1% FBS-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 18:0-acyl-LPG in colon cancer HT29 cells.

[0060] Figure 32 demonstrates that 10% FBS induces LPA2 receptor mediated lamellipodia formation for colon cancer HT29 cells.

[0061] Figure 33 demonstrates that there is no inhibition of 10% FBS-induced LPA2 receptor mediated lamellipodia formation by 10 μ M 18:0-acyl-LPG in colon cancer HT29 cells.

[0062] Figure 34 demonstrates that there is no inhibition of 10% FBS-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 18:0-acyl-LPG in colon cancer HT29 cells.

[0063] Figure 35 demonstrates the inhibition of cell growth (cell viability) at high concentration of 18:0-acyl-LPG in the presence of 10 μ M of 14:0 LPA in colon cancer HT29 cells.

[0064] Figure 36 demonstrates the inhibition of cell growth (cell viability) at high concentration of 18:0-acyl-LPG only in the presence of low concentrations of FBS (1%) but not in the presence of high concentration of FBS (10%) in colon cancer HT29 cells.

[0065] Figure 37 demonstrates LPA2 receptor mediated lamellipodia formation for androgen insensitive prostate cancer PC-3 cells in serum-free medium control.

[0066] Figure 38 demonstrates the effect of 30 μ M 14:0-LPG on LPA2 receptor mediated lamellipodia formation in androgen insensitive prostate cancer PC-3 cells.

[0067] Figure 39 demonstrates the effect of 30 μ M 18:0-acyl-LPG on LPA2 receptor mediated lamellipodia formation in androgen insensitive prostate cancer PC-3 cells.

[0068] Figure 40 demonstrates the effect of 30 μ M 18:1-acyl-LPG on LPA2 receptor mediated lamellipodia formation in androgen insensitive prostate cancer PC-3 cells.

[0069] Figure 41 demonstrates that 18:1 LPA induces LPA2 receptor mediated lamellipodia formation for androgen insensitive prostate cancer PC-3 cells.

[0070] Figure 42 demonstrates the inhibition of 18:1 LPA-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 14:0-acyl-LPG in androgen insensitive prostate cancer PC-3 cells.

[0071] Figure 43 demonstrates the inhibition of 18:1 LPA-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 18:0-acyl-LPG in androgen insensitive prostate cancer PC-3 cells.

[0072] Figure 44 demonstrates the inhibition of 18:1 LPA-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 18:1-acyl-LPG in androgen insensitive prostate cancer PC-3 cells.

[0073] Figure 45 demonstrates the inhibition of cell growth (cell viability) at high concentration of 14:0-acyl-LPG in the presence of 10 μ M of 18:1 LPA in androgen insensitive prostate cancer PC-3 cells.

[0074] Figure 46 demonstrates inhibition of cell growth (cell viability) at high concentration of 18:0-acyl-LPG, and also in the presence of 10 μ M of 18:1 LPA in androgen insensitive prostate cancer PC-3 cells.

[0075] Figure 47 demonstrates inhibition of cell growth (cell viability) at high concentration of 18:1-acyl-LPG, and also in the presence of 10 μ M of 18:1 LPA in androgen insensitive prostate cancer PC-3 cells.

[0076] Figure 48 summarizes the inhibition of cell growth by various LPA derivatives with and without the presence of LPA in androgen insensitive prostate cancer PC-3 cells.

[0077] Figure 49 demonstrates the inhibition of cell growth by various LPA derivatives with and without the presence of LPA in androgen insensitive prostate cancer DU145 cells.

[0078] Figure 50 summarizes the inhibition of cell growth by various LPA derivatives with and without the presence of LPA in androgen insensitive prostate cancer DU145 cells.

[0079] Figure 51 shows that there is no calcium mobilization in the presence of 18:1 LPA in androgen sensitive prostate cancer LNCaP cells.

[0080] Figure 52 demonstrates that there is no phosphorylation of p42 and p44 MAP kinase in the presence of 18:1 LPA in androgen sensitive prostate cancer LNCaP cells.

[0081] Figure 53 demonstrates that there is no inhibition of cell viability in the presence of various LPA derivatives in androgen sensitive prostate cancer LNCaP cells after about 24 hours.

[0082] Figure 54 demonstrates minor inhibition of cell viability in the presence of some LPA derivatives in androgen sensitive prostate cancer LNCaP cells after about 48 hours.

[0083] Figure 55 demonstrates LPA derivatives reduce focal adhesion in androgen insensitive prostate cancer DU145 cells.

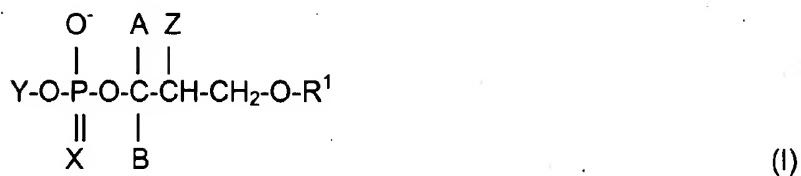
[0084] Figure 56 demonstrates LPA derivatives reduce focal adhesion in androgen insensitive prostate cancer PC-3 cells.

DETAILED DESCRIPTION

[0085] LPA is a phosphatidic acid in which the hydroxyl group of the first carbon of the glycerol is esterified to a fatty acid, the second carbon is not esterified, and the third carbon is bound to a phosphate group, O-PO₃H₂. In the case of a pharmaceutically acceptable salt of the invention, one or more hydrogens are replaced, for example, with sodium ions (Na⁺) and other ions. The first carbon typically contains an acyl ester of fatty acids. Studies on the effects of the presence or absence of LPA and LPA signaling in various types of cells have revealed the involvement of LPA in cancer, cardiovascular functions, ischemia/reperfusion injury, atherosclerosis, wound healing, prevention of toxicity of chemotherapy and radiation therapy, immunological functions, and others. Thus, the design and identification of effectors of LPA signaling may provide novel therapeutic approaches in the management of these pathological states.

I. Structures of compounds

[0086] In one embodiment, the invention provides a compound having the formula (I):



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, A is selected from the group consisting of hydrogen, hydroxyl, and halogen, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, Z is selected from the group consisting of hydrogen, hydroxyl, halogen, haloalkyl, haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, and alkynyloxy, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of hydrogen, halogen, saturated and unsaturated haloalkyl, saturated and

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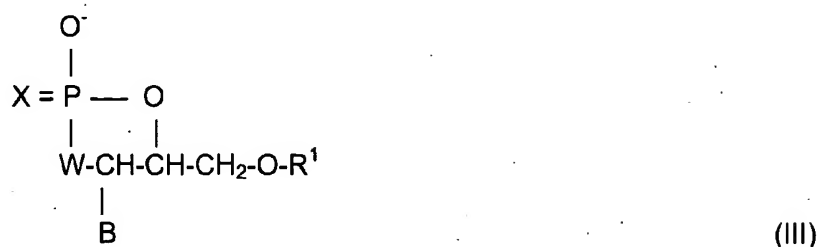
unsaturated haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof, and when X is oxygen and A and B are both hydrogen, then Y is not hydrogen.

[0087] In another embodiment, the invention provides a compound having the formula (II):



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, A is selected from the group consisting of hydrogen, hydroxyl, and halogen, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, Z is selected from the group consisting of hydrogen, hydroxyl, halogen, haloalkyl, haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, and alkynyloxy, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof.

[0088] In still another embodiment, the invention further provides a compound having the formula (III):



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, W is oxygen or a bond, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof.

[0089] The invention provides LPA effectors, derivatives, and/or analogs having the above various general formula. R¹ can be an unsubstituted or substituted, saturated or unsaturated, straight or branched chain alkyl having from about 10 to about 24 carbon atoms. For all of the structures referenced herein, R¹ can have between 0 and (n-2)/2 unsaturated bonds, wherein n is the number of carbon atoms in R¹. Substitutions include, but are not limited to, halogen, hydroxy, phenyl, amino and acylamino. The term "unsaturated" is used in reference to the various structures herein to describe the number of unsaturated carbon atoms in R¹. For example, if R¹ is an eighteen carbon alkyl with one unsaturated carbon-carbon bond at any of the possible carbon-carbon bond, it is herein referred to as 18:1-LPA.

[0090] As used herein, LPA includes LPA having any one of a variety of fatty acids esterified at the C1 position. Examples include LPA wherein the fatty acid ester is lauroyl, myristoyl, palmitoyl, stearoyl, palmitoleoyl, oleoyl, or linoleoyl, among others. For a representative example of suitable phospholipids, the reader is

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directed to any chemical catalog of a phospholipid supplier, for instance, the Avanti Polar Lipids Inc., catalog.

[0091] Suitable "alkyl", "alkenyl", and "alkynyl" is straight or branched, and may contain single, double, triple carbon to carbon bonds of one to twenty five carbon atoms or longer and may include methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, heneicosyl, docosyl, tricosyl, tetracosyl, pentacosyl, lauryl, octadecyl, myristyl, palmityl, stearyl, palmitoleyl, oleyl, linoleyl, linolenyl, eleosteryl, among others.

[0092] Suitable "alkoxy" may include alkyl-O-groups, alkenyl-O-groups, and alkynyl-O-groups, wherein the alkyl, alkenyl, or alkynyl moiety is the same as defined above, but preferably the higher ones, such as octadecyl, myristyl, myristoyl, palmityl, stearyl, palmitoleyl, oleyl, linoleyl, among others. Preferred "alkoxy" for Z may include o-methyl groups.

[0093] Suitable "acyl" may include CO-alkyl, CO-alkenyl, and CO-alkynyl groups, wherein the alkyl, alkenyl, or alkynyl moiety is the same as defined above, but preferably the higher ones, such as dodecoyl, tridecoyl, tetradecoyle, pentadecoyle, hexadecoyle, heptadecoyle, octadecoyle, nonadecoyle, eicosoyle, heneicosoyle, docosoyle, tricosoyle, tetracosoyl, pentacosoyl, lauroyl, octadecoyle, myristoyl, palmitoyl, stearyl, palmitoleyl, oleoyl, linoleoyl, linolenoyl, eleosteroyl, among others.

[0094] Suitable "aryl" may include ring-like functional group having five or more carbon atoms, e.g., benzene, naphthalene, phenanthrene, anthracene, etc. Each carbon of the functional group may be substituted with long or short alkyl chain or others (also called "hetero" substitutions, e.g., hydroxyl and halogen), among others. Suitable "aralkyl" may include both aliphatic and aromatic structures, and may substitute with atoms other than carbon, e.g., alkyl benzenesulfonate, among others.

[0095] Suitable "lower alkoxy substituted with one or more hydroxy groups" may include monohydroxypropoxy, monohydroxybutoxy, monohydroxypentyloxy, monohydroxyhexyloxy, dihydroxypropoxy, 1-hydroxymethyl-2-hydroxyethoxy, 2,3-,

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2,4- or 3,4-dihydroxybutoxy, 2,3,4-trihydroxybutoxy, di-, tri-, tetra- or penta-hydroxypentyloxy, di-, tri-, tetra-, penta- or hexahydroxyhexyloxy, and the like. These hydroxy groups may be protected by protective groups and/or two adjacent hydroxy groups may be protected as a cyclic acetal (e.g., methyleneacetal, ethylideneacetal, benzylideneacetal, isopropylideneacetal, etc.), and the like. The above "lower alkoxy" group may be further substituted with lower alkoxy group(s) (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, etc.).

[0096] Suitable "lower alicyclic-oxy group substituted with one or more hydroxy groups" may include monohydroxycyclobutoxy, monohydroxycyclopentyloxy, monohydroxycyclohexyloxy, 2,3-, 2,4- or 3,4-dihydroxycyclobutoxy, 2,3,4-trihydroxycyclobutoxy, di-, tri- or tetra-hydroxycyclopentyloxy, cis-, epi-, allo-, myo-, muco-, neo, scyllo- or chiro-inosityl, di-, tri-, tetra- or penta-hydroxycyclohexyloxy and the like. The hydroxy groups contained in these groups may be protected with protective groups known in the art.

[0097] Suitable "halogen" or "halo" group may include fluoro, chloro, bromo, and iodine.

[0098] As used herein, "effectors of LPA" encompasses LPA derivatives, antagonists, inhibitors, stimulators, agonists, effectors, modulators, and analogs. Given the examples provided herein, it can be determined readily if an LPA analog exerts a positive or negative effect on the function of a specific LPA receptor or different binding specificity on various LPA receptors, and/or exhibits sufficient growth inhibition or anti-cancer activity suitable for medical use. Suitable LPA derivatives and analogs may be synthesized by methods known in the art and/or are commercially available from various sources, such as Avanti Polar Lipids Inc. from Alabaster, Alabama. For example, effectors of LPA include any of the LPA derivatives/analogues having the formula I, II, or III.

[0099] In one embodiment, LPA derivatives/analogues of the invention include substitutions by small molecules at the sn3 position of the glycerol backbone. One example of such compound is D-3-deoxy-phosphatidyl-*myo*-inositol ether lipid

(DPIEL), having a tri-hydroxyl-*myo*-inositol ring at the sn3 position of the glycerol backbone. However, DPIEL contains an ether linkage at the sn1 position of the glycerol backbone rather than an acyl linkage at the sn1 position of the glycerol backbone like other LPA compounds. Therefore, LPA derivatives/analogs of the invention are designed to include either acyl or ether linkages in order to test their effects on LPA signaling. Further, it is contemplated that small molecule substitutions at the sn3 position of the glycerol backbone of LPA compounds may exhibit an effect on LPA signaling. Such LPA derivatives may be used to test their effects on specific subtype of LPA receptors and, ultimately, their effect for treating a disease, e.g., their ability to stimulate or inhibit cancer growth. Furthermore, it is contemplated that LPA derivatives of the invention with small molecule substitutions at the sn3 position of the glycerol backbone may become more chemically or metabolically stable, more drugable (*i.e.*, structurally stable such that it is suitable to be used as a drug).

[00100] Such LPA derivatives/analogs having small molecule substitutions at the sn3 position of the glycerol backbone may include compounds having the formula I, II, or III, where Y may be an alicyclic ring, including one, di-, tri-, tetra-, penta-, hexahydroxyhexyloxy, and derivatives thereof. In addition, Y may be saturated or unsaturated, straight or branched chain of alkoxy, acyl, aryl, heteroaryl, and aralkyl, having six or more carbon atoms and optionally being substituted with one or more hydroxyl, halo, or lower alkoxy or haloalkyl groups, among others. Exemplary LPA derivatives/analogs include, but are not limited to, 1-lauroyl-sn2-O-methyl-rac-glycero-D-3-deoxy-*myo*-inositol-3-phosphate, 1-myristoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-*myo*-inositol-3-phosphate, 1-palmitoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-*myo*-inositol-3-phosphate, 1-stearoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-*myo*-inositol-3-phosphate, 1-oleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-*myo*-inositol-3-phosphate, 1-linoleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-*myo*-inositol-3-phosphate, 1-linolenoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-*myo*-inositol-3-phosphate, 1-eleosteroyl-sn2-O-methyl-rac-glycero-D-3-deoxy-*myo*-inositol-3-phosphate, and derivatives thereof. Other examples include 1-acyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)] and 1-alkyl-2-hydroxy-sn-glycero-3-[phospho-

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rac-(1-glycerol)], e.g., 1-lauroyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-palmitoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-elesteroyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-lauryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-palmityl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-eleosteryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], and derivatives thereof.

[00101] In addition, compounds having substitutions at the sn1 position are also contemplated. For example, in formula I, II, or III, R¹ may be saturated or unsaturated, substituted or unsubstituted, straight or branched chain of alkyl, alkenyl, alkynyl, and acyl, having six or more carbon atoms, such as an alkyl or acyl having nine or more carbon atoms and including saturated carbon-carbon bonds, one unsaturated carbon bond, and two or more unsaturated carbon bonds, among others.

[00102] Furthermore, compounds having substitutions at the sn2 position are also contemplated. For example, in formula I, II, or III, Z may be hydroxyl, halogen, haloalkyl, haloalkyloxy, alkoxy, alkenyloxy, and alkynyloxy, among others. Preferably, Z may be hydroxyl and methoxy. Such LPA derivatives may further include other substitutions at other positions of the glycerol backbone; for example, X may be sulfur and/or Y may be an alicyclic ring having one, di-, tri-, tetra-, penta-, hexahydroxyhexyloxy, among others. As an example, compounds having R¹ as alkyl, alkenyl, alkynyl or acyl, Z as a hydroxyl group, and Y as halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, alkoxy, alkenyloxy, alkynyloxy, aryl, or aryloxy, optionally substituted with one or more hydroxy or lower alkoxy groups, may be included. As another example, other compounds include those when R¹ is an alkyl, alkenyl, alkynyl or acyl, Z is a methoxy group, and Y is a

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halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, alkoxy, alkenyloxy, alkynyloxy, aryl, heteroaryl, aryloxy, or lower alicyclic-oxy groups, optionally substituted with one or more hydroxy or lower alkoxy groups.

[00103] In another embodiment, the phosphate group in the sn3 position can be substituted with other functional groups, e.g., X and Y. Also, the sn3 position can include a phosphonate group, as represented in formula II and formula III, when W is a bond. For example, the LPA derivatives/analogues of the invention include, but are not limited to, 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-phosphonate, and derivatives thereof.

[00104] Exemplary LPA derivatives/analogues include, but are not limited to, 1-lauryl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-myristyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-palmityl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-stearyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-oleyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-lauryl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-myristyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-palmityl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-stearyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-oleyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-lauroyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-linolenoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-eleosteroyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-lauroyl-

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sn2-O-methyl-rac-glycero-3-phosphonate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-oleoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-phosphonate, and derivatives thereof.

[00105] In another embodiment, when the functional group X is sulfur, the LPA derivatives/analogues of the invention include LPA derivatives having phosphothionate and thiophosphonate groups including, but not limited to, 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 2-alkyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-acyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-acyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

[00106] Exemplary LPA derivatives/analogues further include, but are not limited to, 1-lauryl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-myristyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-palmityl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-stearyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-oleyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-lauryl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-myristyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-palmityl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-stearyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-oleyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-linolenyl-sn2-O-methyl-rac-

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glycero-3-phosphothionate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-phosphothionate, 2-lauryl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-myristyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-palmityl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-stearyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-oleyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-linoleyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-linolenyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-eleosteryl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-lauryl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-myristyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-palmityl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-stearoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-oleyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-linoleyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-linolenyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-eleosteryl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-lauroyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-myristoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-palmitoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-stearoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-oleoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-linoleoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-linolenoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-eleosteryl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-lauroyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-myristoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-palmitoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-stearoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-oleoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-linoleoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-linolenoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-eleosteryl-sn-1-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

[00107] Additional exemplary LPA derivatives/analogs include, but are not limited to, 1-alkyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-

thiophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, and derivatives thereof.

[00108] In another embodiment, LPA derivatives/analogues may include a halogen group at any of the sn1, sn2, sn3 position as represented by Y, R¹, Z, A, and/or B. For example, in the formula I, II, and III, Y can be a halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkoxy, when a halo group includes fluoro, chloro, bromo, and iodine, among others.

[00109] Examples of such LPA derivatives/analogues include, but are not limited to, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphonate, and derivatives thereof.

[00110] Such haloderivatives of LPA analogues include, but are not limited to, 1-alkyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-fluorophosphate,

1-alkynyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-acyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-alkyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-acyl-sn2-O-methyl-rac-glycero-3-bromophosphate, and derivatives thereof.

[00111] Additionally, 1-lauryl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-myristyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-palmityl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-stearyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-oleyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-lauryl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-myristyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-palmityl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-stearyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-oleyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-linolenoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-eleosteroyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-oleoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-eleosteroyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, and derivatives thereof may be included.

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[00112] Other examples may include 1-lauryl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-myristyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-palmityl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-stearyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-oleyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-lauryl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-myristyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-palmityl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-stearyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-oleyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-lauroyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-linolenoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-eleosteroyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-oleoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-eleosteroyl-sn2-O-methyl-rac-glycero-3-bromophosphate, and derivatives thereof.

[00113] Further, LPA derivatives, such as 1-lauryl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-myristyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-palmityl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-stearyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-oleyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-

fluorophosphonate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-stearyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-oleyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-lauroyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-linolenoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-eleosteroyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-oleoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-eleosteroyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, and derivatives thereof, may be included.

[00114] Additional LPA derivatives include 1-lauryl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-myristyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-palmityl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-stearyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-oleyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-lauryl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-myristyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-palmityl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-stearyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-oleyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-lauroyl-sn2-hydroxide-rac-glycero-3-

bromophosphonate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-linolenoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-eleosteroyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-oleoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-eleosteroyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, and derivatives thereof.

[00115] In still another embodiment, in the formula I, II, and III, each of A and B may be independently a hydrogen, hydroxyl, halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, when a halo group includes fluoro, chloro, bromo, and iodine, among others. Such haloderivatives of LPA analogs include, but are not limited to, 1-alkyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphate, 1-alkenyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphate, 1-alkynyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphate, 1-acyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphate, 1-alkyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphate, 1-alkenyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphate, 1-alkynyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphate, 1-acyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphate, 1-alkyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphothionate, 1-acyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphothionate, 1-alkyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphonate, 1-acyl-

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sn2-hydroxide-sn3-halo-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphonate, and derivatives thereof.

[00116] In addition, A and B may both be a halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkoxy, among others, including 1-alkyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphate, 1-alkenyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphate, 1-alkynyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphate, 1-acyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphate, 1-alkyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphate, 1-alkenyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphate, 1-alkynyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphate, 1-acyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphate, 1-alkyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphothionate, 1-acyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphonate, 1-acyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphonate, and derivatives thereof.

[00117] In still another embodiment, it is further contemplated that compounds of LPA derivatives may contain substitutions at both sn2 and sn3 positions to include cyclic glycerol derivatives, such as 1-alkyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-acyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-

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alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof, among others.

[00118] Pharmaceutically acceptable salts of the phospholipids encompassed by the present invention, include, but are not limited to, free acid forms, alkali metal salts, such as sodium and potassium, alkaline earth metal salts, such as calcium and magnesium, non-toxic heavy metal salts, ammonium salts, trialkylammonium salts, such as trimethyl-ammonium and triethylammonium, and alkoxyammonium salts, such as triethanolammonium, tri(2-hydroxyethyl)ammonium, and tromethamine (tris(hydroxymethyl)aminomethane). Particularly preferred are sodium and ammonium salts.

[00119] Mimetics encompassed by the present invention, include, but are not limited to, synthetic compounds that are developed using the biological system of LPA signaling. Stereoisomers encompassed by the present invention, include, but are not limited to, compounds that have the same kinds and numbers of atoms but have different molecular arrangements. Enantiomers encompassed by the present invention, include, but are not limited to, a pair of chiral isomers (e.g., R and S isomers) that are direct, nonsuperimposable mirror images of each other.

[00120] Derivatives and analogs encompassed by the present invention, include, but are not limited to, substitutions on any of the R, X, Y, and Z groups, such as, among others, saturated or unsaturated alkyl derivatives, straight or branched derivatives, mimetics, stereoisomers, and enantiomers thereof.

II. Obtaining the Compounds

[00121] A suitable LPA derivative can be obtained from any source including, but not limited to, commercially available phospholipids, isolated from a variety of

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different plants (including plant organs) and animals, and/or created synthetically. Preferably the plants are in the soybean family, but the phospholipids can be isolated from other plants including, but not limited to, those in the leguminosae (beans and peas, etc.). The phospholipids can also be isolated from partially purified plant extracts including, but not limited to, soy molasses, lecithin (fluid, deoiled or other forms), partially purified protein concentrates, partially purified protein hydrolysates, defatted soy flakes, refined soy oils, soy grits, soy flours and other soy fractions from which lipids can be extracted. An example of lipid extraction from soybeans may be found in U.S. Pat. No. 3,365,440. In addition, U.S. Pat. Nos. 5,567,425; 5,602,885; 5,624,675; 5,635,186; 5,635,187 include general descriptions of a variety of techniques useful in the art for synthesizing and obtaining phospholipid compounds.

[00122] The LPA derivative can be obtained from plant sources by any method known in the art, provided it results in purification of at least one of the phospholipids of the invention. A variety of methods for purifying and analyzing phospholipids from plant sources are described in Bligh and Dyer (1959) *Can. J. Biochem. Physiol.* 37:911-917; Patton et al. (1982) *J. Lipid Res.* 23:190-196; Jungalwala (1985) *Recent Developments in Techniques for Phospholipid Analysis*, in *Phospholipids in Nervous Tissues* (ed. Eichberg) John Wiley and Sons, pp. 1-44; Hamilton et al. (1992) in the series, *A Practical Approach* (Rickwood et al. eds.) IRL Press at Oxford University Press; and Kates (1986) *Techniques of Lipidology: Isolation, Analysis and Identification in Laboratory Techniques in Biochemistry and Molecular Biology* (Burdon et al. eds.) Elsevier.

[00123] The LPA derivative can also be derived from animal sources. Preferably, the animal is a mammal. Even more preferably, the phospholipids are derived from liver cells. Such phospholipids are commercially available or can be purified from animal tissue by methods known in the art, for instance from animal and egg lecithin or from the compositions described in WO 95/15173, which is incorporated herein by reference. Phospholipids in general, and LPAs in particular, can also be derived from blood.

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[00124] The LPA derivative of the invention can also be synthesized by methods known in the art. Suitable semi-synthetic phospholipids and their synthesis are described in Kates, *Techniques of Lipidology* (1972). For example, a synthesis of lysophosphatidic acid is described in W. Stoffel and G. D. Wolf, *Chemische Synthese von 1-O-[3H]Palmitoyl-L-glycerin-3-phosphate (L-3-Lysophosphatidsaure)*, Chem. Ber., 347 (1966) 94-101. As another example, the synthesis of various cyclic phosphate LPAs is described in A. J. Slotboom, et al., *Synthesis of Lysophosphoglycerides*, Chem. Phys. Lipids, 1 (1967) 317-336; PCT Publication No. WO 92/21323; and U.S. Pat. No. 5,565,439, which are incorporated herein by reference.

[00125] Procedures for synthesis of functionalized glycerol ether derivatives which can be used in the synthesis of compounds suitable for use in the present invention are described in K. Agarwal, et al., *Synthesis of carbamyl and ether analogs of phosphatidylcholines*, Chem. Phys. Lipids, 39 (1984) 169-177, and H. Eibl and P. Woolley, *A general synthetic method for enantiomerically pure ester and ether lysophospholipids*, Chem. Phys. Lipids, 47 (1988) 63-68. A method for the preparation of lysophosphatidic acid or lysophosphatidates by reacting glycidyl esters with anhydrous phosphoric acid is described in U.S. Pat. No. 3,423,440.

III. LPA derivatives/analogues as LPA receptor subtype specific inhibitor

[00126] In one embodiment, the invention provides selective effectors, such as agonists and/or antagonists for various LPA receptor subtypes, such as LPA1, LPA2, LPA3, and the like.

1. LPA receptor subtypes for LPA signaling

[00127] The biological responses to various LPAs are mediated by specific members of the LPA receptor family, such as LPA1, LPA2, LPA3 and LPA4 receptors. These receptors exhibit high affinity for LPAs (e.g., LPA14:0, LPA 18:1, etc.) and their expression levels may vary among different cells. For example, LPA 1 is widely expressed in normal cells and cancer cells, such as the ovarian cancer cell line, OVCAR3, the prostate cancer cell line, PC-3, and the like. LPA2 and LPA3 are

expressed at low levels, if at all, in normal adult tissues. However, LPA2 and LPA3 are present in some cancer cell lines, such as ovarian cancer cell lines (OVCAR3) and prostate cancer cell lines (e.g., PC-3 and DU145). For example, ovarian cancer OVCAR3 cells express high levels of LPA3 mRNA. As shown in Figure 10, quantitative-PCR analysis indicates that OVCAR3 cells express a high level of LPA3 mRNA, a medium level of LPA2 mRNA, a low level of LPA1 mRNA, and negligible expression level of LPA4 mRNA, whereas colon cancer HT29 cells express medium level of LPA2 mRNA and negligible expression levels of LPA1, LPA3, and LPA4 mRNA.

[00128] In addition, the invention provides evidence that LPA1, LPA2, and LPA3 mRNA and protein expression are present in prostate cancer cell lines through RT-PCR and functional calcium mobilization assays, as described in more detail below. In contrast, LPA4 mRNA is not expressed in the prostate cancer cell line PC-3, eliminating it as a target for LPA signaling in prostate cancer cells. Further, transcriptional profiling data using Affymetrix arrays demonstrates expression of LPA1, LPA2, and LPA3 directly in prostate cancer patients. Thus, LPA2 and LPA3 may be attractive targets for the design and testing of novel therapeutic compounds for cancer therapy.

[00129] It has been observed that 14:0 LPA is an LPA2 selective agonist that stimulates LPA2 signaling, whereas 18:1 LPA is a pan LPA agonist that stimulates LPA1, LPA2, and LPA3 signaling. In addition, an LPA analog, 1-acyl-sn2-O-methyl-rac-glycero-3-phosphothionate (OMPT) stimulates LPA3 signaling and is thus a selective LPA3 agonist. These findings are confirmed by a calcium mobilization assay, which measures changes in intracellular calcium concentration, $[Ca^{2+}]$, which acts as a surrogate for receptor activation since calcium is an important intracellular mediator and LPA is a potent activator for increases in cytosolic calcium. OMPT efficiently activates calcium mobilization in LPA3 expressing insect sf9 cells. OMPT also enhances GTP $[\gamma\text{-}^{35}\text{S}]$ binding in the cell membrane of HEK293 T cells expressing LPA3. Each of lysophospholipids desensitized calcium mobilization,

suggesting that the effects of lysophospholipids are mediated by G-protein coupled LPA receptors.

[00130] For example, calcium mobilization assays for these LPA lysophospholipids can be tested in insect cells, e.g., sf9 cells, which do not contain LPA receptors in their genome, to provide a sensitive and selective model for dissecting LPA signaling. It has been observed that a LPA analog, OMPT, is a selective LPA3 agonist since OMPT increases intracellular calcium concentration with an EC_{50} of 69 nM, > 10,000 nM, and > 10,000 nM in sf9 insect cells expressing extraneous LPA3, LPA1, and LPA2 receptor cDNAs, respectively. In addition, 18:1 LPA is an agonist for LPA2 and LPA3, since 18:1 LPA increases intracellular calcium concentration with an EC_{50} of 0.84 nM and 76 nM in sf9 insect cells expressing extraneous LPA2 and LPA3 receptor cDNAs, respectively. On the other hand, 14:0 LPA is a selective LPA2 agonist, since 14:0 LPA increases intracellular calcium concentration with an EC_{50} of 0.1 nM in sf9 insect cells expressing extraneous LPA2 receptor cDNA. However, no elevated intracellular calcium concentration is observed in 14:0 LPA treated sf9 insect cells expressing extraneous LPA1 and LPA3 receptor cDNA. Thus, OMPT and 14:0 LPA serve as selective effectors for LPA3 and LPA2 receptors, respectively.

[00131] The procedures for these calcium mobilization assays are as followed: OVACR3 cells and PC-3 cells were cultured in RPMI 1640 medium with 10% FBS (fetal bovine serum). HT29 cells were cultured in DMEM(high glucose) medium with 10% FBS. All cells were cultured at about 37 °C in a humidified atmosphere with 5% CO₂. After starvation in serum-free medium for about 12-24 hours, cells were harvested and loaded with about 1 μ M of Indo-1 AM in serum-free medium for about 45 min at 37 °C. Cells were washed in PBS and resuspended at 2×10^6 cells/ml in a $[Ca^{2+}]_i$ assay buffer (Sodium chloride, NaCl, about 140 mM, potassium chloride, KCl, about 2mM, magnesium chloride, MgCl₂, about 1mM, calcium chloride, CaCl₂, about 2 mM, in about 25 mM HEPES buffer at pH 7.4 with about 10 mM of glucose). Cytoplasmic $[Ca^{2+}]_i$ was determined at an excitation wavelength of about 331 nm and an emission wavelength of 410 nm using a fluorescence

spectrophotometer (Hitachi, F-4000). Approximately 3×10^6 cells were used for $[Ca^{2+}]_i$ determination in a stirred quartz cuvette kept at about 37 °C. OMPT or 18:1 LPA was dissolved in about 0.1% BSA/PBS solution and applied immediately to the cells. To test other LPA derivatives of the invention, cells were exposed to the derivatives for about 3 minutes or for a period of various times in time course related experiments before a LPA agonist, such as 18:1 LPA, OMPT, or other LPAs was applied into the cuvette.

[00132] The results of a typical calcium mobilization assay are shown in Figure 3. Figure 3 demonstrates the effect of OMPT-induced and 18:1 LPA-induced calcium mobilization in ovarian cancer cells (OVCAR3) and colon cancer cells (HT29). As shown in Figure 3, 18:1 LPA, but not OMPT, stimulates calcium mobilization in HT29 cells. Figure 4 demonstrates the concentration-response curves of OMPT and 18:1 LPA on calcium mobilization in OVCAR3 and HT29 cells. The open circles indicate OMPT induction in OVCAR3 cells. The closed circles indicate OMPT induction in HT29 cells. The closed triangles indicate 18:1 LPA induction in HT29 cells. The EC_{50} values of OMPT and 18:1 LPA in HT29 cells are less than about 1 μ M and about 22.1 nM (about 8.2 to about 59.2 nM), respectively. The EC_{50} values of OMPT in OVCAR3 cells is about 9.0 nM (about 7.0 nM to about 11.5 nM). Thus, LPA3 is not expressed in HT29 cells.

2. Structures of LPA and LPA derivatives/analogs

[00133] The structure of a representative LPA is shown in Figure 1. The structure of D-3-deoxy-phosphatidyl-*myo*-inositol ether lipid (DPIEL) and a representative losophosphatidyl glycerol (LPG) are shown in Figure 2A and 2B, respectively. Structurally, DPIEL and LPG are derivatives/analogs of LPA. In one embodiment, the invention provides a variety of LPA derivatives/analogs in order to test their functions as effectors, agonists, and/or antagonists for LPA signaling through the interaction with specific LPA receptor subtypes.

[00134] As shown in Figure 1, LPA has a phosphatidic acid at the *sn*3 position, a hydroxyl group at the *sn*2 position, and an acyl-linkage fatty acid (such as 18:1 or

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14:0 as shown) at the *sn*1 position of the glycerol backbone. As shown in Figure 2A, D-3-deoxy-phosphatidyl-*myo*-inositol ether lipid (DPIEL) has a phosphatidyl-*myo*-inositol at the *sn*3 position and an alkyl ether-linkage fatty acid (18:0) at the *sn*1 position of the glycerol backbone. Thus, DPIEL is an LPA analogue. It has been reported that DPIEL is an inhibitor of a serine/threonine protooncogene protein kinase, referred to as AKT. It is thought that the phosphatidyl-*myo*-inositol structure at the *sn*3 position of DPIEL binds to PH2 domain of AKT protein. However, the pharmacological functions of substitutions at *sn*2 and *sn*1 fatty acid positions are not known. DPIEL can be purchased from Calbiochem (San Diego, CA, USA).

[00135] DPIEL is related in structure to LPG (lysophosphatidyl glycerol). As shown in Figure 2B, LPG has a phosphatidylglycerol at the *sn*3 position, a hydroxyl group at the *sn*2 position, and an alkyl-linkage fatty acid (such as 18:0 as shown) at the *sn*1 position of the glycerol backbone. We have confirmed that LPG is an inhibitor of LPA signaling in human Jurkat T cells without testing the receptor subtype specificity (Xu Y., Casey, G., and Mills, G. B., 1995 *Lysophospholipids activate the human Jurkat T cell line*. J. Cell Physiol. 163:441-450, Xu, Y., Fang, X.F., Casey, G., and Mills, G.B., 1995 *Lysophospholipids activate ovarian and breast cancer cells*. Biochem J. 309:933-940.). The invention further provides evidence that LPG has similar activities to DPIEL in decreasing signaling through specific LPA receptors. In addition, we have published a novel method to make stable derivatives of LPA, such as OMPT, as LPA receptor specific agonists (Hasegawa Y, Erickson JR, Goddard GJ, Yu S, Liu S, Cheng KW, Eder A, Bandoh K, Aoki J, Jarosz R, Schrier AD, Lynch KR, Mills GB, Fang X. 2003 *Identification of a phosphothionate analogue of lysophosphatidic acid as a selective agonist of the LPA3 receptor*. J. Biol. Chem. 278:11962-9).

[00136] In one embodiment, to develop selective LPA effectors, agonists, and/or antagonists, the invention provides synthesized LPA analogues. Since DPIEL is shown herein as a selective LPA3 antagonist, initially, DPIEL related analogues with methoxyl at the *sn*2, and an alkyl, alkenyl, or alkynyl linkage at the *sn*1 position may be used, which will enhance LPA receptor subtype selectivity. To establish selective LPA receptor subtype effectors, replacement of phosphatidyl-*myo*-inositol at the *sn*3

position may be necessary. To test this hypothesis, LPG was screened. LPG has a phosphatidylglycerol at the *sn3* position and an acyl-linked fatty acid at the *sn1* position. For example, various LPG (e.g., those shown in Figure 9, 14:0 LPG and 18:0 LPG, 18:1 LPG, etc.) can be used to test their activity as effectors for selective LPA receptor subtypes. It is hypothesized that replacement of phosphatidyl-myoinositol with other structures, such as a phosphatidylglycerol group and others as described above, at the *sn3* position will lead to reduced AKT inhibiting activity, and thus reduced crosstalk between LPA signaling and AKT signaling. Based on the structure-activity relationship, LPA derivatives, such as derivatives of DPIEL and LPG, which strongly agonize or antagonize LPA-receptor interaction and enhance or reduce cell growth, are identified. In one embodiment, the invention confirms that different LPA derivatives, such as 14:0 LPG and 18:0 LPG, 18:1 LPG, inhibit different LPA receptor subtypes. In another embodiment, the invention provides effectors which reduce cell-viability of androgen-independent prostate cancer DU145 and PC-3 cells, but not that of androgen-dependent prostate cancer LNCaP cells.

3. Design of subtype selective effectors for LPA receptors

[00137] In yet another embodiment, the invention provides a series of LPA derivatives and establishes the structure-bioactivity relationship of the LPA derivatives, which may signal through LPA receptor subtypes. Applicants propose that: unsaturated fatty acids with at least an 18-carbon length at the *sn1* position of the glycerol backbone in the structure of LPA are required for optimal LPA3 binding; a saturated fatty acid is preferable for LPA1 and LPA2 binding; a free hydroxide at *sn2* position in LPA structure is critical for LPA2 binding; and short carbon length fatty acids at the *sn1* position are preferable for LPA1 binding. Derivatives/analogues of LPA, DPIEL, LPG may be synthesized to determine whether the alkyl, alkenyl, or alkynyl-fatty acid linkage group, or the myo-inositol structure is required for LPA signaling. For example, derivatives with *sn2*-OH group may preferably antagonize LPA2 signaling, whereas derivatives with *sn2*-OCH₃ and *sn1*-alkenyl unsaturated fatty acid may selectively antagonize LPA3 signaling. In addition, derivatives with *sn2*-OH and *sn1* short chain saturated fatty acid may antagonize LPA1 signaling.

[00138] Furthermore, it is contemplated that the above compounds can further include small molecule substitutions at the *sn*3 position of the glycerol backbone in order to generate LPA derivatives that are more chemically or metabolically stable, more drug-like (*i.e.*, structurally stable to have a long half-life *in vivo* and suitable to be used as a drug). Exemplary small molecule substitutions at the *sn*3 position to be screened for LPA receptor subtype specificity can be found in the structures and compounds of the invention as described above. For example, substitutions at the *sn*3 position such that in the formula I, II, or III, Y is a halo group may help to stabilize the LPA derivatives synthesized. Similarly, substitutions with a halo group can also be at the *sn*2 position in order to generate a stable LPA derivative.

[00139] Therefore, effects of the LPA derivatives of the invention may be assayed by the LPA-induced calcium mobilization assay as mentioned above and also in insect sf9 cells, which do not express LPA receptors, with LPA1, LPA2, or LPA3 exogenously expressed. Accordingly, 14:0 (myristoyl) LPG, 18:0 (stearoyl) LPG, and 18:1 (oleoyl) LPG, purchased from Avanti Polar Lipids (Alabaster, AL, USA), were screened. In addition, suitable drugs candidates designed based on the structures of LPA and LPA receptor as positive or negative effectors/regulators for LPA signaling can be assayed accordingly in order to test their ability to bind to LPA receptors and increase and/or inhibit LPA signaling. The results of these assays can help to develop drugs for cancer treatment.

4. Identification of subtype selective effectors for LPA receptors

[00140] We demonstrate that D-3-deoxy-phosphatidyl-*myo*-inositol ether lipid (DPIEL) inhibits LPA response in ovarian cancer OVCAR3 and androgen-independent prostate cancer PC-3 and DU145 cells. The ovarian cancer OVCAR3 cell line is characterized by a high level of LPA3 mRNA expression. Figure 5 demonstrates the effect of DPIEL on LPA-induced calcium mobilization in OVCAR3 cells. The left panels reflect absolute cytoplasmic calcium concentration change and the right panels reflect the relative cytoplasmic calcium change. OMPT was applied in OVCAR3 cells after exposure of the cells to DPIEL for about 3 minutes. OMPT

was cumulatively applied to OVCAR3 cells which were exposed to DPIEL throughout the whole experiment.

[00141] As shown in Figure 5, after exposure to DPIEL (10 μ M or 20 μ M), the concentration-dependent calcium mobilization curve induced by OMPT, which is the LPA3 selective agonist, has shifted 10 fold toward the right in OVCAR3 cells as observed by the direct calcium concentration change or the relative change in calcium concentration as compared to the no DPIEL control. Notably, the maximum responses in both control and DPIEL (10 μ M) exposed groups are not changed [control group: about 123.5 \pm 16.4 nM (N=4), DPIEL (about 10 μ M) exposed group: about 136.1 \pm 16.6 nM], suggesting that DPIEL competitively antagonizes the LPA3 receptor. Also shown in Figure 5, at about 20 μ M of DPIEL, the LPA derivative, DPIEL, shifted the concentration-dependent curves about 50 fold toward to the right with about 36% suppression of the maximum response concentration.

[00142] Figure 6 demonstrates the effect of DPIEL on LPA-induced calcium mobilization in HT29 cells. The left panels reflect absolute cytoplasmic calcium concentration change and the right panels reflect the relative cytoplasmic calcium change. 18:1 LPA was applied to HT29 cells after exposure of the cells to DPIEL for about 3 minutes. 18:1 LPA was cumulatively applied to HT29 cells, which were exposed to DPIEL throughout the experiment. In colon cancer HT29 cells that express only the LPA2 receptor and as shown in Figure 6, DPIEL does not inhibit calcium mobilization induced by 18:1 LPA. Accordingly, these results indicate that LPA2 is not a target receptor of DPIEL and the inhibition of LPA signaling by DPIEL is selective to LPA3.

[00143] Figure 7 demonstrates the effect of DPIEL on LPA-induced calcium mobilization in PC-3 cells. The left panels reflect absolute cytoplasmic calcium concentration change and the right panels reflect the relative cytoplasmic calcium change. 18:1 LPA was applied to PC-3 cells after exposure of the cells to DPIEL for about 3 minutes. 18:1 LPA was cumulatively applied to PC-3 cells, which were exposed to DPIEL throughout the experiment. In human androgen-independent prostate cancer PC-3 cells, which express high level of LPA1 and low levels of LPA2

and LPA3, DPIEL suppress the maximum calcium mobilization induced by 18:1 LPA (a pan LPA agonist) for about 56%, as shown in Figure 7. The concentration-dependent curve of calcium mobilization induced by 18:1 LPA is not shifted, and the ED 50 on the relative concentration-dependent curve of Figure 7 for a 18:1 LPA-induced calcium mobilization assay is not changed. Accordingly, these results suggest that DPIEL can non-competitively inhibit an LPA1-mediated LPA response in addition to specific inhibition mediated by LPA3.

[00144] DPIEL has been reported to inhibit AKT protein activity due to the presence of its *myo*-inositol structure. Here, we demonstrate that DPIEL inhibits phosphorylation of vasodilator stimulated protein (VASP) and LPA-induced migration in androgen-independent prostate cancer PC-3 cells, suggesting that DPIEL is a potential candidate as an LPA antagonist. We have studied the time course of phosphorylation levels of AKT and ERK introduced as exogeneous genes on a plasmid in OVCAR3 cells and the effect of phosphorylation levels of AKT and extracellular signal-regulating kinase (ERK) introduced as exogeneous genes on a plasmid in OVCAR3 cells induced with OMPT. For these kinase related phosphorylation experiments, cells were pre-treated with DPIEL for about 30 minutes and then exposed to LPA derivative, such as OMPT, 18:1 LPA, or 14:0 LPA for 10 minutes after starvation in serum-free medium for about 12 to 24 hours. The cells were then lysed in SDA sample buffer or ice-cold X-100 lysis buffer (1% Triton X-100, 50mM HEPES [pH7.4], 150mM NaCl, 1.5mM MgCl₂, 1mM EGTA, 10% glycerol, 100mM NaF, 10mM Na pyrophosphate, and 1mM aprotinin). Total cellular protein was resolved by SDS/PAGE, transferred to immobilon [poly (vinylidene difluoride)], and immunoblotted with antibodies following the protocols provided by manufactures. Immunocomplexes were visualized with an enhanced chemiluminescence detection kit (Amersham Pharmacia) using horseradish peroxidase-conjugated secondary antibodies (Bio-Rad).

[00145] Figure 8 demonstrates the effect of DPIEL and/or 18:1 LPA on phosphorylation levels of AKT and ERK introduced exogeneously on a plasmid in PC-3 cells. The cells were first exposed to DPIEL for about 30 minutes and then stimulated by OMPT and/or 18:1 LPA as indicated for about 10 minutes.

[00146] As shown in Figure 8, DPIEL inhibits phosphorylation of the extracellular signal-regulating kinase (ERK) activated by both 18:1 LPA and 14:0 LPA in androgen-independent prostate cancer DU145 and PC-3 cells. Interestingly, the level of inhibition of AKT phosphorylation is very weak, compared with the level of inhibition of ERK phosphorylation. As shown in Figure 8, the effect of DPIEL on ERK signaling is more prominent than found in previous studies for the effect of DPIEL on AKT signaling and apoptosis. The exposure of DPIEL in this invention is only for about 30 minutes, while previous experiments by others typically include an exposure time of at least about 16 to 24 hours. Accordingly, these results demonstrate that the inhibition of ERK phosphorylation by such a LPA derivative is faster and more efficient than AKT phosphorylation and other signaling events. The results further demonstrate that DPIEL is a potential candidate for prostate cancer therapy as a LPA antagonist.

[00147] It has been observed that 14:0 LPG and 18:0 LPG inhibited calcium mobilization induced by 14:0 LPA, an $LPA_{1/2}$ agonist, in DU145 cells. It has been observed that 18:0 LPG, but not 14:0 LPG, inhibited LPA-induced calcium mobilization in colon cancer HT29 cells (which only express LPA_2), which suggests that 14:0 LPG may be a LPA_1 antagonist and that 18:0 LPG may be a $LPA_{1/2}$ antagonist. It has also been observed that 18:1 LPG completely antagonized 18:1 LPA, a pan LPA receptor agonist, in DU145 cells, which suggests that 18:1 LPG may be a $LPA_{1/2/3}$ antagonist.

[00148] Given the major role of LPA in the growth, viability, neovascularization, and metastases of multiple cell lineages, effectors of LPA signaling are potential therapeutic compounds for the treatment of cancer and other diseases. Other suitable applications include cardiovascular functions, ischemia/reperfusion injury, atherosclerosis, wound healing, prevention of toxicity of chemotherapy and radiation therapy, immunological functions, among others.

5. Determine whether LPA receptors are targets for therapy in androgen-independent prostate cancer

[00149] In order to determine the role of specific LPA receptors in prostate cancer cells and to validate them as therapeutic targets, it is necessary to develop a series of receptor-selective agonists and antagonists. For this purpose, a LPA3 selective agonist, 1-acyl-*sn*2-O-methyl-*rac*-glycero-3-phosphothionate (OMPT) was first characterized.

[00150] In androgen-independent prostate cancer PC-3 cell line, 18:1 LPA stimulates calcium mobilization with an EC₅₀ of about 5nM. The LPA2 selective ligand, 14:0 LPA, stimulates calcium mobilization with an EC₅₀ of about 98 nM; whereas the LPA3 selective ligand, OMPT, stimulates calcium mobilization with an EC₅₀ of about 117 nM. Accordingly, these results suggest the presence of functional G-protein coupled LPA receptors in PC-3 cells.

[00151] To further evaluate the functionality of LPA receptors in androgen-independent prostate cancer PC-3 and DU145 cells, we demonstrate that 18:1 LPA activates AKT, p38-, and p42/p44-MAPK as indicated by increased reactivity with phosphospecific antibodies. The selective LPA3 ligand, OMPT, efficiently activates AKT and p42/p44-MAPK but not p38-MAPK. In contrast, the LPA_{1/2} ligand 14:0 LPA efficiently activates p42/p44-MAPK, but only marginal effects on AKT and p38. Accordingly, these results indicate that different LPA receptors couple to specific downstream signaling pathways in prostate cancer cells.

[00152] It has been observed that 18:1 LPA and OMPT increase cellular proliferation and prevent growth factor withdrawal-induced apoptosis. The results are consistent with their selective effects on signaling in prostate cancer cells. Accordingly, these results suggest that the LPA3 receptor is crucial for cell-proliferation in PC-3 cells. On the other hand, 14:0 LPA does not increase cellular proliferation and prevent growth factor withdrawal-induced apoptosis.

[00153] To further evaluate the functionality of LPA receptors in PC-3 cells, it has been observed that 18:1 LPA (a pan agonist) and 14:0 LPA (a LPA2 specific

agonist) stimulate membrane ruffling and cell migration in PC-3 cells, which suggests that LPA_{1/2} receptor is critical to cell migration in androgen-independent prostate cancer cells. In contrast, OMPT (a LPA₃ selective agonist) induces neither morphology changes nor migration, supporting OMPT's receptor subtype selective properties.

[00154] To determine the mechanisms regulating LPA-induced cell migration, actin filament binding proteins that link receptor signaling to lamellipodia formation were evaluated. For example, 18:1 LPA and 14:0 LPA induced phosphorylation of vasodilator-stimulated protein (VASP), an actin filament capping protein, at the Ser157 PKA phosphorylation site, which suggests that LPA stimulates lamellipodia formation by stabilizing actin filament polymerization. Neither OMPT nor EGF increased phosphorylation of VASP. H-89, a protein kinase A (PKA) inhibitor, completely inhibited membrane ruffling and cell migration induced by 18:1 LPA and 14:0 LPA, which suggests that PKA mediates LPA_{1/2} receptor-stimulated cell migration.

[00155] Compatible with the effects on cell migration, 18:1 LPA and 14:0 LPA efficiently activate PKA, however, OMPT does not. To further assess whether LPA₂ contributes to membrane ruffling, PC-3 cells stably overexpressing LPA₂ are generated. Strikingly, these PC-3 cells that are overexpressing LPA₂ receptor acquire a round shape with constitutive membrane ruffling, typically associated with constitutive VASP phosphorylation at the Ser 157 PKA phosphorylation site. These results suggest that LPA₂ may be sufficient to mediate lamellipodia formation leading to cell migration.

[00156] To further evaluate the mechanism by which LPA mediates its functions in prostate cancer, the LPA transcriptome is identified through transcriptional profiling. Subsequently, the fact that LPA increases interleukin-8 (IL-8) transcription and stimulates IL-8 secretion is verified. The results suggest that IL-8, which is a potent mediator for neovascularization, proliferation, and migration in PC-3 cells, may contribute to LPA-induced cell migration in PC-3 cells.

[00157] In addition, indirect immunofluorescence data suggest that phosphorylated VASP localizes to the tip of the actin filament in lamellipodia, whereas LPA2 and CXCR-1 (IL-8 receptor) co-localize in ruffling membranes. The results suggest that LPA 2 receptor may play a crucial role in initiating cell migration in PC-3 cells. Further, upon knockdown of VASP protein by short double-stranded RNA interference (siRNA), LPA-induced migration in PC-3 cells is reduced, which suggests that phosphorylation of VASP is critical to LPA-induced migration in androgen-independent prostate cancer.

[00158] To further evaluate the function of LPA in androgen-independent prostate cancer, the selective LPA hydrolyzing enzyme, lysophosphatidic acid phosphatase, and the lysophosphatidylcholine hydrolyzing enzyme, lysoPLD, may be knocked down in androgen-independent prostate cancer PC-3 and DU145 cells in order to evaluate the resulting phenotypical changes.

6. Determine the role of the androgen receptor in the regulation of LPA receptor expression and function

[00159] In androgen-dependent prostate cancers, androgen is sufficient for the survival and proliferation of prostate cancer cells. Functional androgen receptors repress the ability of LPA to stimulate cells either through inhibition of downstream signaling or inhibition of functional LPA receptor expression. Under hormonal ablation therapy, LPA becomes critical to the proliferation and survival of the prostate cancer cells through the expression of various functional LPA receptors or unmasking of LPA signal transduction. The LPA2 receptor may mediate migration, whereas the LPA3 receptor may mediate survival and proliferation in androgen-independent prostate cancer cells. Suppression of LPA mRNA expression or LPA signaling may lead to novel effective therapeutic approaches to prostate cancer.

[00160] LPA receptors are expressed in androgen-sensitive prostate cancer LNCaP cells and androgen-insensitive prostate cancer cells, such as DU145 and PC-3 cells. Strikingly, in androgen-sensitive prostate cancer LNCaP cells, despite the presence of mRNA for LPA receptors, LPA does not induce the increase of

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intracellular calcium concentration or activate kinases, such as p42-MAPK, p44-MAPK, p38 MAPK or JNK. Nor does LPA induce proliferation or prevent cell death in LNCaP cells. In contrast, LPA activates increases in intracellular calcium concentration, p42-MAPK, p44-MAPK, and cell proliferation in androgen-insensitive prostate cancer DU145 and PC-3 cells. The results suggest that the presence of androgen receptor may contribute to the inability of LPA to activate LNCaP cells.

[00161] To assess whether the presence of the androgen receptor contributes to the inability of LPA to activate LNCaP cells, the androgen receptor in PC-3 cells is stably expressed. Strikingly, the introduction of the androgen receptor into PC-3 cells completely blocks the ability of LPA and OMPT to activate PC-3 cells and alter the signaling for survival or proliferation, as indicated by changes in cytosolic calcium, phosphorylation of intracellular targets, induction of proliferation and prevention of apoptosis. Thus, it appears that the androgen receptor modulates the function of LPA receptors.

[00162] To further evaluate the role of the androgen receptor in the regulation of LPA receptor, the androgen receptor may be knocked down in androgen-dependent prostate cancer LNCaP cells by siRNA to evaluate the changes in LPA signaling in these cells. In addition, the androgen receptor can be transfected into another androgen-independent prostate cancer cell line, the DU145 cell line, to evaluate changes in LPA signaling.

[00163] In summary, the functionalities of LPA in androgen-insensitive prostate cancer cells have been demonstrated. For example, in DU145 and PC-3 cells, the LPA2 receptor mediates cell migration, whereas LPA3 receptor mediates prolongation of cell viability. In addition, in androgen-insensitive prostate cancer DU145 and PC-3 cells, DPIEL inhibits the activation of p42-MAPK and p44-MAPK, and LPA-induced cell migration.

7. Determine if LPA antagonists are effective in androgen-independent prostate cancer

[00164] As indicated above, the androgen-independent prostate cell line PC-3 can be induced to proliferate by LPA and LPA agonists. In addition, LPA increases cell migration in PC-3 cells. These results suggest that the LPA signaling pathway may mediate proliferation and migration of androgen-independent prostate cancer cells. These results further suggest that the LPA2 receptor may mediate migration, whereas the LPA3 receptor may mediate proliferation in androgen-independent prostate cancer cells.

[00165] Further, it has been observed that D-3-deoxy-phosphatidyl-myoinositol ether lipid (DPIEL) inhibits the LPA response in ovarian cancer OVCAR3 and androgen-independent prostate cancer PC-3 and DU145 cells. Thus, embodiments of the invention identify the pathophysiological function of LPA receptors in prostate cancer cells and provide important data support and rationale for the design of potential novel therapeutic approaches to cancer therapy in general and specific types of androgen-independent prostate cancers. Most importantly, embodiments of the invention provide information related to the conversion of prostate cancer cells to androgen-independence.

[00166] Effectors of LPA signaling that selectively agonize and/or antagonize LPA signaling may be assessed for their effects on LPA-induced cell growth, cell migration, and IL-8 production in androgen-independent prostate DU145 and PC-3 cells according to the techniques described above.

[00167] In addition, it has been observed that when LPA derivatives, such as various LPGs are screened, 18:0 LPG and 18:1 LPG, but not 14:0 LPG reduced cell viability of DU145 and PC-3 cells. In androgen-sensitive and LPA-insensitive prostate cancer LNCaP cells, LPG did not reduce cell viability, which suggests that LPG is a selective LPA inhibitor. 18:0 LPG could reduce cell migration of androgen-insensitive prostate cancer DU145 cells. Thus, these results suggest that inhibitors

to LPA receptors will lead to new approaches for androgen-insensitive prostate cancer therapy.

[00168] The results are shown in Figures 9-56. Figure 9 illustrates chemical structures of various LPGs, including 14:0 LPG, 18:0 LPG, and 18:1 LPG exemplified herein. The 14:0, 18:0, 18:1 represents the structures of the fatty acid chain at the sn3 position of the glycerol backbone. Figure 10 shows the mRNA expression levels of various LPA receptors in different cancer cells as described above. As shown in Figure 10, LPA2 and LPA3 are suitable targets to design LPA derivatives affecting LPA signaling.

[00169] Figure 11 is a graph showing inhibition of calcium mobilization of 14:0 LPA by 14:0 LPG in DU145 cancer cells. In each experiment, 14:0 LPA or 14:0 LPG was cumulatively added to the cells. Figure 12 demonstrates inhibition of 14:0 LPA signaling by 14:0 LPG in DU145 cancer cells. Figure 13 demonstrates normalized response of the inhibition of 14:0 LPA signaling by 14:0 LPG in DU145 cancer cell. The EC₅₀ value is about 50.9 nM. The results suggest that 14:0 LPG is an effective inhibitor/antagonist for 14:0 LPA-induced signaling in DU145 cancer cells.

[00170] Figure 14 is a graph showing 18:1 LPA-induced calcium mobilization in DU145 cancer cell. Figure 15 is a graph showing 18:1 LPA-induced calcium mobilization in the presence of 10 μ M 18:1-acyl-LPG in DU145 cancer cells. Figure 16 is a graph showing 18:1 LPA-induced calcium mobilization in the presence of 30 μ M 18:1-acyl-LPG in DU145 cancer cells. Figure 17 demonstrates concentration-dependent inhibition of 18:1 LPA signaling by 18:1-acyl-LPG in DU145 cancer cells. Figure 18 demonstrates a normalized response of the inhibition of 18:1 LPA signaling by 18:1-acyl-LPG in DU145 cancer cells. The results suggest that 18:1 LPG is an effective inhibitor/antagonist for 18:1 LPA-induced signaling in DU145 cancer cells.

[00171] Figure 19 demonstrates the effect of 14:0 LPG and 18:1-acyl-LPG on OMPT-induced calcium mobilization in androgen insensitive prostate cancer PC-3 cells. Figure 20 demonstrates the normalized response of the inhibition of 14:0 LPG

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and 18:1-acyl-LPG on OMPT-induced calcium mobilization in androgen insensitive prostate cancer PC-3 cells. The results suggest that 18:1 LPG is an effective inhibitor/antagonist for 18:1 LPA-induced signaling in PC-3 cancer cells.

[00172] Figure 21 demonstrates the effect of 14:0 LPG, 18:0 LPG, and 18:1-acyl-LPG on 18:1 LPA-induced calcium mobilization in colon cancer HT29 cells. Figure 22 demonstrates a normalized response of the inhibition of 14:0 LPG, 18:0 LPG, and 18:1-acyl-LPG on 18:1 LPA-induced calcium mobilization in colon cancer HT29 cells. The results suggest that 18:0 LPG and 18:1 LPG, but not 14:0 LPG, are effective inhibitors/antagonists for 18:1 LPA-induced signaling in PC-3 cancer cells.

[00173] Figure 23 demonstrates LPA2 receptor mediated lamellipodia formation for colon cancer HT29 cells in serum-free medium control. Figure 24 demonstrates the effect of 10 μ M 18:0-acyl-LPG on serum-starvation mediated lamellipodia formation in colon cancer HT29 cells. Figure 25 demonstrates the effect of 30 μ M 18:0-acyl-LPG on serum-starvation mediated lamellipodia formation in colon cancer HT29 cells. The results suggest that 18:0 LPG inhibits serum-starvation induced signaling in HT29 cancer cells.

[00174] Figure 26 demonstrates 14:0 LPA induces LPA2 receptor mediated lamellipodia formation for colon cancer HT29 cells. Figure 27 demonstrates the inhibition of 14:0 LPA-induced LPA2 receptor mediated lamellipodia formation by 10 μ M 18:0-acyl-LPG in colon cancer HT29 cells. Figure 28 demonstrates the inhibition of 14:0 LPA-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 18:0-acyl-LPG in colon cancer HT29 cells. The results suggest that 18:0 LPG inhibits LPA2-induced signaling in HT29 cancer cells.

[00175] Figure 29 demonstrates 1% fetal bovine serum (FBS) induces LPA2 receptor mediated lamellipodia formation in colon cancer HT29 cells. Figure 30 demonstrates the inhibition of 1% FBS-induced LPA2 receptor mediated lamellipodia formation by 10 μ M 18:0-acyl-LPG in colon cancer HT29 cells. Figure 31 demonstrates the inhibition of 1% FBS-induced LPA2 receptor mediated

lamellipodia formation by 30 μ M 18:0-acyl-LPG in colon cancer HT29 cells. The results suggest that 18:0 LPG inhibits LPA2-induced signaling in HT29 cancer cells.

[00176] Figure 32 demonstrates 10% FBS induces LPA2 receptor mediated lamellipodia formation for colon cancer HT29 cells. Figure 33 demonstrates no inhibition of 10% FBS-induced LPA2 receptor mediated lamellipodia formation by 10 μ M 18:0-acyl-LPG in colon cancer HT29 cells. Figure 34 demonstrates no inhibition of 10% FBS-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 18:0-acyl-LPG in colon cancer HT29 cells.

[00177] Figure 35 demonstrates inhibition of cell growth (cell viability) at high concentrations of 18:0-acyl-LPG even in the presence of 10 μ M of 14:0 LPA in colon cancer HT29 cells. Figure 36 demonstrates inhibition of cell growth (cell viability) at high concentration of 18:0-acyl-LPG only in the presence of low concentration of FBS (1%) but not in the presence of high concentrations of FBS (10%) in colon cancer HT29 cells.

[00178] Figure 37 demonstrates LPA2 receptor mediated lamellipodia formation for androgen insensitive prostate cancer PC-3 cells in serum-free medium control. Figure 38 demonstrates the effect of 30 μ M 14:0-LPG on LPA2 receptor mediated lamellipodia formation in androgen insensitive prostate cancer PC-3 cells. Figure 39 demonstrates the effect of 30 μ M 18:0-acyl-LPG on LPA2 receptor mediated lamellipodia formation in androgen insensitive prostate cancer PC-3 cells. Figure 40 demonstrates the effect of 30 μ M 18:1-acyl-LPG on LPA2 receptor mediated lamellipodia formation in androgen insensitive prostate cancer PC-3 cells.

[00179] Figure 41 demonstrates 18:1 LPA induces LPA2 receptor mediated lamellipodia formation for androgen insensitive prostate cancer PC-3 cells. Figure 42 demonstrates the inhibition of 18:1 LPA-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 14:0-acyl-LPG in androgen insensitive prostate cancer PC-3 cells. Figure 43 demonstrates the inhibition of 18:1 LPA-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 18:0-acyl-LPG in androgen insensitive prostate cancer PC-3 cells. Figure 44 demonstrates the inhibition of 18:1

LPA-induced LPA2 receptor mediated lamellipodia formation by 30 μ M 18:1-acyl-LPG in androgen insensitive prostate cancer PC-3 cells.

[00180] Figure 45 demonstrates inhibition of cell growth (cell viability) at high concentrations of 14:0-acyl-LPG in the presence of 10 μ M of 18:1 LPA in androgen insensitive prostate cancer PC-3 cells. Figure 46 demonstrates inhibition of cell growth (cell viability) at high concentrations of 18:0-acyl-LPG, and also in the presence of 10 μ M of 18:1 LPA in androgen insensitive prostate cancer PC-3 cells. Figure 47 demonstrates inhibition of cell growth (cell viability) at high concentrations of 18:1-acyl-LPG, and also in the presence of 10 μ M of 18:1 LPA in androgen insensitive prostate cancer PC-3 cells.

[00181] Figure 48 summarizes the inhibition of cell growth by various LPA derivatives with and without the presence of LPA in androgen insensitive prostate cancer PC-3 cells. Figure 49 demonstrates the inhibition of cell growth by various LPA derivatives with and without the presence of LPA in androgen insensitive prostate cancer DU145 cells. Figure 50 summarizes the inhibition of cell growth by various LPA derivatives with and without the presence of LPA in androgen insensitive prostate cancer DU145 cells.

[00182] Figure 51 shows no calcium mobilization in the presence of 18:1 LPA in androgen sensitive prostate cancer LNCaP cells. Figure 52 demonstrates no phosphorylation of p42 and p44 MAP kinase in the presence of 18:1 LPA in androgen sensitive prostate cancer LNCaP cells. Figure 53 demonstrates no decrease in cell viability in the presence of various LPA derivatives in androgen sensitive prostate cancer LNCaP cells after about 24 hours. Figure 54 demonstrates a minor reduction of cell viability in the presence of some LPA derivatives in androgen sensitive prostate cancer LNCaP cells after about 48 hours.

[00183] Figure 55 demonstrates LPA derivatives reduce focal adhesion in androgen insensitive prostate cancer DU145 cells. Figure 56 demonstrates LPA derivatives reduce focal adhesion in androgen insensitive prostate cancer PC-3 cells.

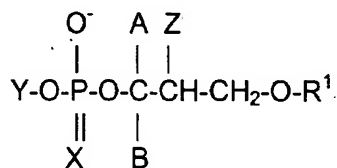
8. *in vivo* pre-clinical pharmacology and animal studies

[00184] Effective DPIEL derivatives and LPG derivatives are assessed in *in vivo* anti-tumor models for their ability to inhibit solid tumor growth, such as prostate tumor growth. As an example, prostate cancer cell lines, PC-3 and DU145 cells, are implanted subcutaneously or by other means in SCID nude mice. Intraperitoneal injection of compounds of the invention is followed after tumor inoculation. No injection of the compounds is performed as a control. Compounds of the invention can also be delivered by other methods known in the art. These approaches allow assessment of the effectors of LPA signaling on PC-3 and DU145 cells. Tumor growth is measured by the size and/or volume (e.g., in MM3) of the solid tumor developed at the site of the implant of cancer cells of the SCID mice. Anti-tumor and/or tumor promoting activity of the compounds of the invention are observed in comparison with the control without the injection of the compounds using statistical analysis of Bonferroni's multiple t-test, followed by ANOVA.

[00185] While the foregoing is directed to embodiments of the present invention, other and further embodiments of the invention may be devised without departing from the basic scope thereof, and the scope thereof is determined by the claims that follow.

WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, A is selected from the group consisting of hydrogen, hydroxyl, and halogen, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, Z is selected from the group consisting of hydrogen, hydroxyl, halogen, haloalkyl, haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, and alkynyloxy, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of hydrogen, halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, and pharmaceutically acceptable salt thereof, and when X is oxygen and A and B are both hydrogen, then Y is not hydrogen.

2. The compound of claim 1, wherein Y is selected from the group consisting of halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, where a halo group is selected from the group consisting of fluoro, chloro, bromo, and iodine; or a mimetic, stereoisomer, enantiomer, or pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein Y is selected from the group consisting of saturated or unsaturated, straight or branched chain of alkoxy, acyl, aryl, heteroaryl,

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and aralkyl, having six or more carbon atoms and optionally being substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, or pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein Y is an alicyclic ring selected from the group consisting of one, di-, tri-, tetra-, penta-, hexahydroxyhexyloxy, and derivatives thereof.

5. The compound of claim 1, wherein X is sulfur.

6. The compound of claim 5, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

7. The compound of claim 6, wherein the compound is selected from the group consisting of 1-lauryl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-myristyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-palmityl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-stearyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-oleyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-lauryl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-myristyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-palmityl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-stearyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-oleyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

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8. The compound of claim 5, wherein the compound is selected from the group consisting of 2-alkyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-acyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-acyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

9. The compound of claim 8, wherein the compound is selected from the group consisting of 2-lauryl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-myristyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-palmityl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-stearyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-oleyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-linoleyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-linolenyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-eleosteryl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-lauryl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-myristyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-palmityl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-stearoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-oleyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-linoleyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-linolenyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-eleosteryl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-lauroyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-myristoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-palmitoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-stearoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-oleoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-linoleoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-linolenoyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-eleosteroyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-lauroyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-myristoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-palmitoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-stearoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-oleoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-linoleoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-

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linolenoyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-eleosteroyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

10. The compound of claim 1, wherein Y is halogen selected from the group consisting of fluoro, chloro, bromo, and iodine.

11. The compound of claim 10, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, and derivatives thereof.

12. The compound of claim 11, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-acyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-alkyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-alkynyl-sn2-O-methyl-rac-

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glycero-3-bromophosphate, 1-acyl-sn2-O-methyl-rac-glycero-3-bromophosphate, and derivatives thereof.

13. The compound of claim 11, wherein the compound is selected from the group consisting of 1-lauryl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-myristyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-palmityl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-stearyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-oleyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-lauryl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-myristyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-palmityl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-stearyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-oleyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-linolenoyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-eleosteroyl-sn2-hydroxide-rac-glycero-3-fluorophosphate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-oleoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, 1-eleosteroyl-sn2-O-methyl-rac-glycero-3-fluorophosphate, and derivatives thereof.

14. The compound of claim 11, wherein the compound is selected from the group consisting of 1-lauryl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-myristyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-palmityl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-stearyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-oleyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-linoleyl-sn2-hydroxide-rac-glycero-

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3-bromophosphate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-lauryl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-myristyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-palmityl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-stearyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-oleyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-lauroyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-linolenoyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-eleosteroyl-sn2-hydroxide-rac-glycero-3-bromophosphate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-oleoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-bromophosphate, 1-eleosteroyl-sn2-O-methyl-rac-glycero-3-bromophosphate, and derivatives thereof.

15. The compound of claim 1, wherein R¹ is selected from the group consisting of saturated or unsaturated, substituted or unsubstituted, straight or branched chain of alkyl, alkenyl, alkynyl, and acyl, having six or more carbon atoms; or a mimetic, stereoisomer, enantiomer, or pharmaceutically acceptable salt thereof.

16. The compound of claim 15, wherein R¹ comprises an alkyl or acyl having nine or more carbon atoms selected from the group consisting of saturated carbon-carbon bonds, one unsaturated carbon bond, two or more unsaturated carbon bonds, and derivatives thereof.

17. The compound of claim 1, wherein Z is selected from the group consisting of hydroxyl, halogen, haloakyl, haloalkyloxy, alkoxy, alkenyloxy, and alkynyloxy.

18. The compound of claim 17, wherein Z is selected from the group consisting of hydroxyl and methoxyl.

19. The compound of claim 18, wherein X is sulfur.

20. The compound of claim 19, wherein Y is an alicyclic ring selected from the group consisting of one, di-, tri-, tetra-, penta-, hexahydroxyhexyloxy, and derivatives thereof.

21. The compound of claim 1, wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl and acyl, Z is a hydroxyl group, and Y is selected from the group consisting of halogen, saturated and unsaturated haloakyl, saturated and unsaturated haloalkyloxy, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, which are optionally substituted with one or more hydroxy or lower alkoxy groups, and derivatives thereof.

22. The compound of claim 1, wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl and acyl, Z is a methoxyl group, and Y is selected from the group consisting of halogen, saturated and unsaturated haloakyl, saturated and unsaturated haloalkyloxy, alkoxy, alkenyloxy, alkynyloxy, aryl, heteroaryl, aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, or pharmaceutically acceptable salt thereof.

23. The compound of claim 22, wherein Y is an alicyclic ring selected from the group consisting of one, di-, tri-, tetra-, penta-, hexahydroxyhexyloxy, and derivatives thereof.

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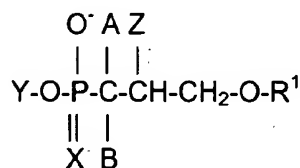
24. The compound of claim 1, wherein A and B are each independently selected from the group consisting of hydrogen, hydroxyl, and halogen, and the compound comprises a halogen group selected from the group consisting of fluoro, chloro, bromo, and iodine.

25. The compound of claim 24, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphate, 1-alkenyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphate, 1-alkynyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphate, 1-acyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphate, 1-alkyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphate, 1-alkenyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphate, 1-alkynyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphate, 1-acyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphate, 1-alkyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphothionate, 1-acyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphothionate, 1-alkyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphonate, 1-acyl-sn2-hydroxide-sn3-halo-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-sn3-halo-rac-glycero-3-phosphonate and derivatives thereof.

26. The compound of claim 24, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphate, 1-alkenyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphate, 1-alkynyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphate, 1-acyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphate, 1-alkyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphate, 1-alkenyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphate, 1-alkynyl-sn2-O-methyl-sn3-dihalo-

rac-glycero-3-phosphate, 1-acyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphate, 1-alkyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphothionate, 1-acyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphothionate, 1-alkyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphonate, 1-acyl-sn2-hydroxide-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-sn3-dihalo-rac-glycero-3-phosphonate and derivatives thereof.

27. A compound having the formula:



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, A is selected from the group consisting of hydrogen, hydroxyl, and halogen, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, Z is selected from the group consisting of hydrogen, hydroxyl, halogen, haloalkyl, haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, and alkynyloxy, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl,

aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, or pharmaceutically acceptable salt thereof.

28. The compound of claim 27, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-phosphonate, and derivatives thereof.

29. The compound of claim 28, wherein the compound is selected from the group consisting of 1-lauryl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-myristyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-palmityl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-stearyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-oleyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-lauryl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-myristyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-palmityl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-stearyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-oleyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-lauroyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-linolenoyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-eleosteroyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-oleoyl-sn2-O-

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methyl-rac-glycero-3-phosphonate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-phosphonate, and derivatives thereof.

30. The compound of claim 27, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphonate, and derivatives thereof, wherein the compound comprises a halogen group selected from the group consisting of fluoro, chloro, bromo, and iodine.

31. The compound of claim 30, wherein the compound is selected from the group consisting of 1-lauryl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-myristyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-palmityl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-stearyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-oleyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-palmityl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-stearyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-oleyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-lauroyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-linolenoyl-sn2-

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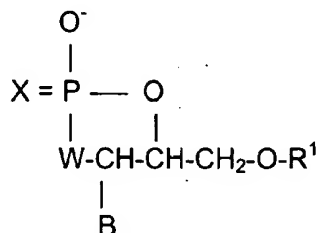
hydroxide-rac-glycero-3-fluorophosphonate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-fluorophosphonate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-oleoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-fluorophosphonate, and derivatives thereof.

32. The compound of claim 30, wherein the compound is selected from the group consisting of 1-lauryl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-myristyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-palmityl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-stearyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-oleyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-linoleyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-linolenyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-lauryl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-myristyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-palmityl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-stearyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-oleyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-linoleyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-linolenyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-eleosteryl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-lauroyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-myristoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-palmitoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-stearoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-oleoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-linoleoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-linolenoyl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-eleosteryl-sn2-hydroxide-rac-glycero-3-bromophosphonate, 1-lauroyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-myristoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-palmitoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-stearoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-oleoyl-sn2-O-methyl-rac-glycero-3-

bromophosphonate, 1-linoleoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-linolenoyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, 1-elesteroyl-sn2-O-methyl-rac-glycero-3-bromophosphonate, and derivatives thereof.

33. The compound of claim 27, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-thiophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-thiophosphonate, and derivatives thereof.

34. A compound having the formula:



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, W is oxygen or a bond, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of halogen, saturated and unsaturated haloalkyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, or pharmaceutically acceptable salt thereof.

35. The compound of claim 34, wherein the compound is selected from the group consisting of 1-alkyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-acyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

36. The compound of claim 34, wherein the compound is selected from the group consisting of 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

37. The compound of claim 34, wherein B is a halogen selected from the group consisting of fluoro, chloro, bromo, and iodine.

38. A pharmaceutical composition for treating a disease, comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

39. The pharmaceutical composition of claim 38, wherein the disease comprises ovarian cancer, androgen insensitive prostate cancer, or colon cancer.

40. A pharmaceutical composition for treating a disease, comprising a therapeutically effective amount of the compound of claim 27 and a pharmaceutically acceptable carrier or excipient.

41. The pharmaceutical composition of claim 39, wherein the disease comprises ovarian cancer, androgen insensitive prostate cancer, or colon cancer.

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42. A pharmaceutical composition for treating a disease, comprising a therapeutically effective amount of the compound of claim 34 and a pharmaceutically acceptable carrier or excipient.

43. The pharmaceutical composition of claim 42, wherein the disease comprises ovarian cancer, androgen insensitive prostate cancer, or colon cancer.

44. A method for treating a disease, comprising administering a pharmaceutically effective amount of the compound of claim 1 to a subject.

45. The method of claim 44, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

46. The method of claim 44, wherein the compound is selected from the group consisting of 2-alkyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-acyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-acyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

47. The method of claim 44, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-acyl-sn2-O-

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methyl-rac-glycero-3-halophosphate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphonate, and derivatives thereof.

48. The method of claim 44, wherein the compound is selected from the group consisting of 1-lauroyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-myristoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-palmitoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-stearoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-oleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-linoleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-linolenoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-eleosteroyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, and derivatives thereof.

49. The method of claim 44, wherein the compound is selected from the group consisting of 1-acyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-lauroyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-palmitoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-

glycerol)], 1-elesteroyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], and derivatives thereof.

50. The method of claim 44, wherein the compound is selected from the group consisting of 1-alkyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-lauryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-palmityl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-eleosteryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], and derivatives thereof.

51. The method of claim 44, wherein the disease comprises a cancer disease.

52. The method of claim 51, wherein the cancer disease is selected from the group consisting of ovarian cancer, androgen insensitive prostate cancer, and colon cancer.

53. A method for treating a disease, comprising administering a pharmaceutically effective amount of the compound of claim 27 to a subject.

54. The method of claim 53, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-phosphonate, and derivatives thereof.

55. The method of claim 53, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-

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hydroxide-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphonate, and derivatives thereof, where the compound comprises a halogen group selected from the group consisting of fluoro, chloro, bromo, and iodine.

56. The method of claim 53, wherein the disease comprises a cancer disease.

57. A method for treating a disease, comprising administering a pharmaceutically effective amount of the compound of claim 34 to a subject.

58. The method of claim 57, wherein the compound is selected from the group consisting of 1-alkyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-acyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

59. The method of claim 57, wherein the compound is selected from the group consisting of 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

60. The method of claim 57, wherein the disease comprises a cancer disease.

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61. A method for treating an androgen insensitive prostate cancer, comprising administering a pharmaceutically effective amount of a compound of a LPA derivative to a subject.

62. The method of claim 61, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

63. The method of claim 61, wherein the compound is selected from the group consisting of 2-alkyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-acyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-acyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

64. The method of claim 61, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-acyl-sn2-O-methyl-rac-

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glycero-3-halophosphothionate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphonate, and derivatives thereof.

65. The method of claim 61, wherein the compound is selected from the group consisting of 1-lauroyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-myristoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-palmitoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-stearoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-oleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-linoleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-linolenoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-eleosteryl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, and derivatives thereof.

66. The method of claim 61, wherein the compound is selected from the group consisting of 1-acyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-lauroyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-palmitoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-eleosteryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], and derivatives thereof.

67. The method of claim 61, wherein the compound is selected from the group consisting of 1-alkyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-lauryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristyl-2-hydroxy-sn-glycero-

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3-[phospho-rac-(1-glycerol)], 1-palmityl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-eleosteryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], and derivatives thereof.

68. The method of claim 61, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-phosphonate, and derivatives thereof.

69. The method of claim 61, wherein the compound is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphonate, and derivatives thereof, where the compound comprises a halogen group selected from the group consisting of fluoro, chloro, bromo, and iodine.

70. The method of claim 61, wherein the compound is selected from the group consisting of 1-alkyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-acyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

71. The method of claim 61, wherein the compound is selected from the group consisting of 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

72. A method for treating a cancer disease, comprising administering a pharmaceutically effective amount of a LPA derivative to bind to a specific subtype of LPA receptor and inhibit cell growth.

73. The method of claim 72, wherein the cancer disease comprises ovarian cancer, androgen insensitive prostate cancer, or colon cancer.

74. The method of claim 72, wherein the LPA derivative is selected from the group consisting of DPEL, lysophosphatidylglycerol, and their derivatives.

75. The method of claim 72, wherein the specific subtype of LPA receptor is selected from the group consisting of LPA1, LPA2, LPA3, and homologs thereof.

76. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

77. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 2-alkyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-hydroxide-rac-glycero-3-

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phosphothionate, 2-acyl-sn-1-hydroxide-rac-glycero-3-phosphothionate, 2-alkyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkenyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-alkynyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, 2-acyl-sn-1-O-methyl-rac-glycero-3-phosphothionate, and derivatives thereof.

78. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphothionate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphothionate, 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphonate, and derivatives thereof.

79. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 1-lauroyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-myristoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-palmitoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-stearoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-oleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-linoleoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-

linolenoyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, 1-
eleosteroyl-sn2-O-methyl-rac-glycero-D-3-deoxy-myo-inositol-3-phosphate, and
derivatives thereof.

80. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 1-acyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-lauroyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-palmitoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenoyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-eleosteroyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], and derivatives thereof.

81. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 1-alkyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-lauryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-myristyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-palmityl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-stearyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-oleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linoleyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-linolenyl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], 1-eleosteryl-2-hydroxy-sn-glycero-3-[phospho-rac-(1-glycerol)], and derivatives thereof.

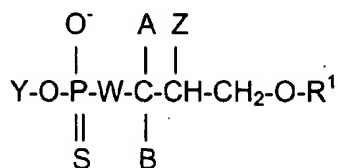
82. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-phosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-phosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-phosphonate, and derivatives thereof.

83. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 1-alkyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-acyl-sn2-hydroxide-rac-glycero-3-halophosphonate, 1-alkyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkenyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-alkynyl-sn2-O-methyl-rac-glycero-3-halophosphonate, 1-acyl-sn2-O-methyl-rac-glycero-3-halophosphonate, and derivatives thereof, where a halo group is selected from the group consisting of fluoro, chloro, bromo, and iodine.

84. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 1-alkyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-acyl-sn2,3-cyclic-glycero-3-phosphothionate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

85. The method of claim 72, wherein the LPA derivative is selected from the group consisting of 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkenyl-sn2,3-cyclic-glycero-3-phosphonate, 1-alkynyl-sn2,3-cyclic-glycero-3-phosphonate, 1-acyl-sn2,3-cyclic-glycero-3-phosphonate, and derivatives thereof.

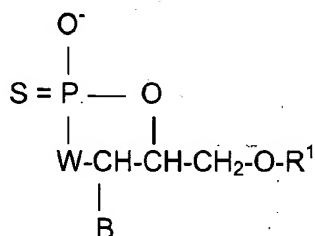
86. A compound having the formula:



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl,

heteroaryloxy, aralkyl, aralkyloxy, A is selected from the group consisting of hydrogen, hydroxyl, and halogen, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, W is oxygen or a bond, Z is selected from the group consisting of halogen, haloakyl, haloalkyloxy, alkyl, alkenyl, alkylanyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, and alkynyloxy, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of hydrogen, halogen, saturated and unsaturated haloakyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkylanyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, or pharmaceutically acceptable salt thereof.

87. A compound having the formula:



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkylanyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, B is selected from the group consisting of hydrogen, hydroxyl, and halogen, W is oxygen or a bond, X is selected from the group consisting of oxygen and sulfur, Y is selected from the group consisting of halogen, saturated and unsaturated haloakyl, saturated and unsaturated haloalkyloxy, alkyl, alkenyl, alkylanyl, saturated acyl, unsaturated acyl, alkoxy, alkenyloxy, alkynyloxy, aryl, aryloxy, heteroaryl, heteroaryloxy, aralkyl, aralkyloxy, substituted aryloxy, and lower alicyclic-oxy groups which are optionally substituted with one or more hydroxy or lower alkoxy groups; or a mimetic, stereoisomer, enantiomer, or pharmaceutically acceptable salt thereof.

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ABSTRACT OF THE DISCLOSURE

The present invention provides compounds and pharmaceutical compositions involved in LPA signaling and methods of treating a disease using compounds and compositions of the invention.

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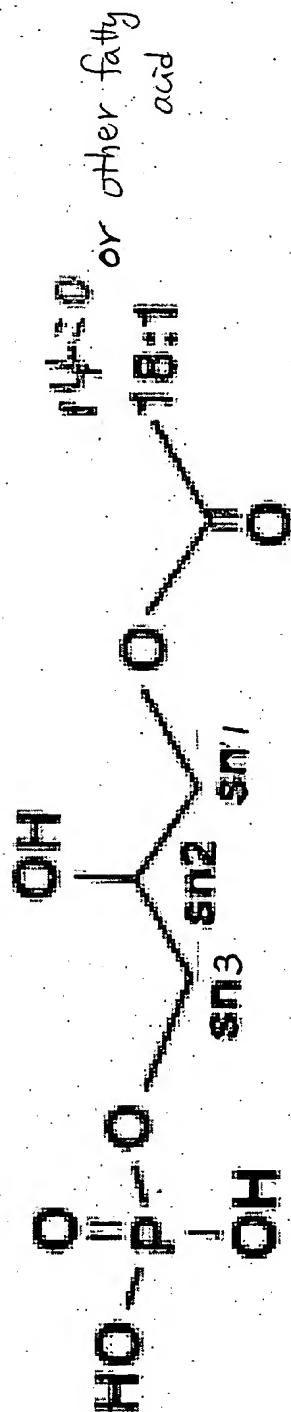


Figure 1

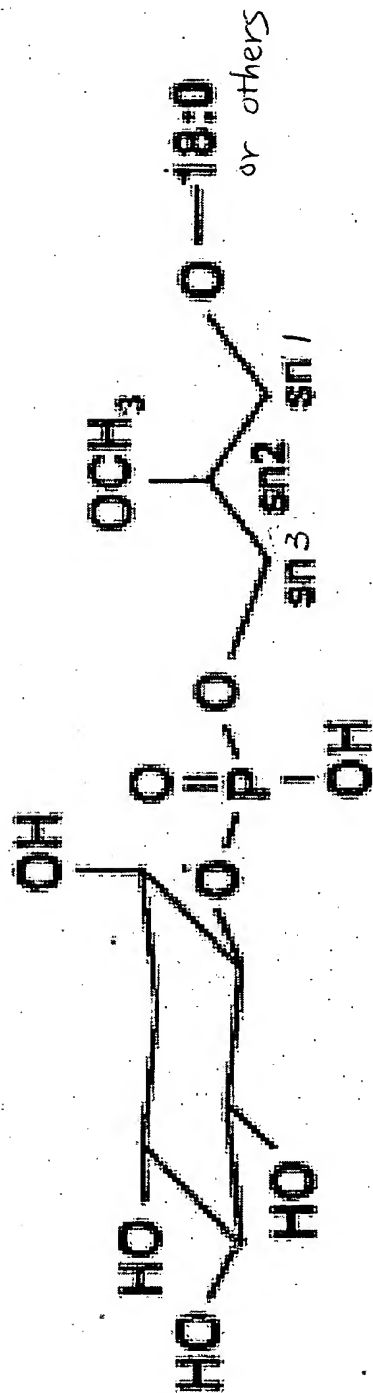


Figure 2A

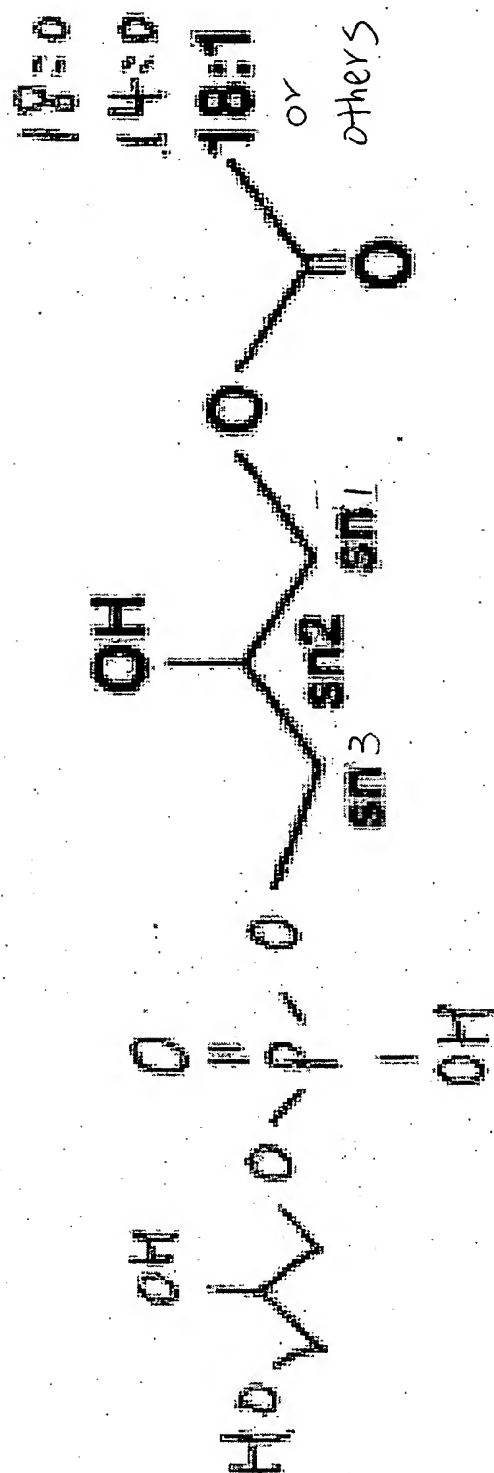


Figure 2B

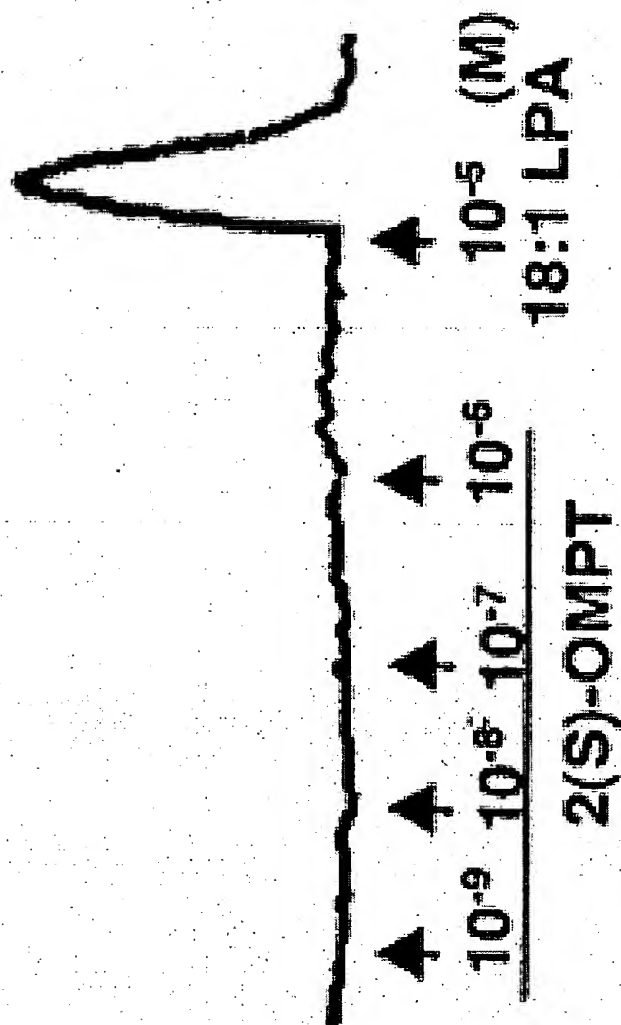


Figure 3

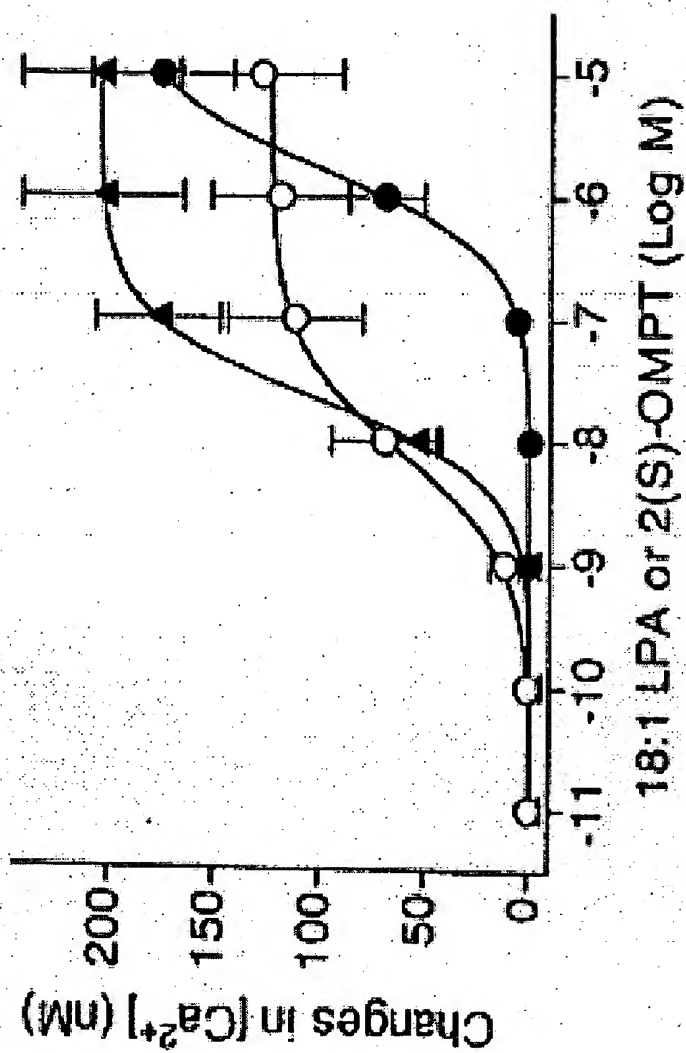


Figure 4

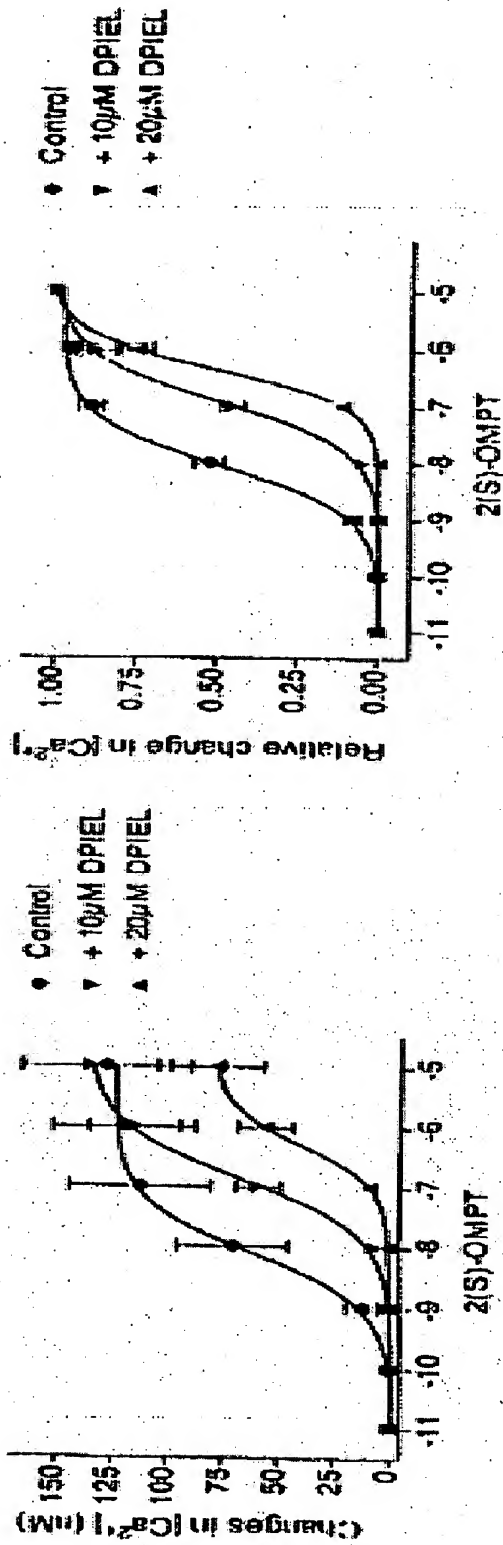


Figure 5

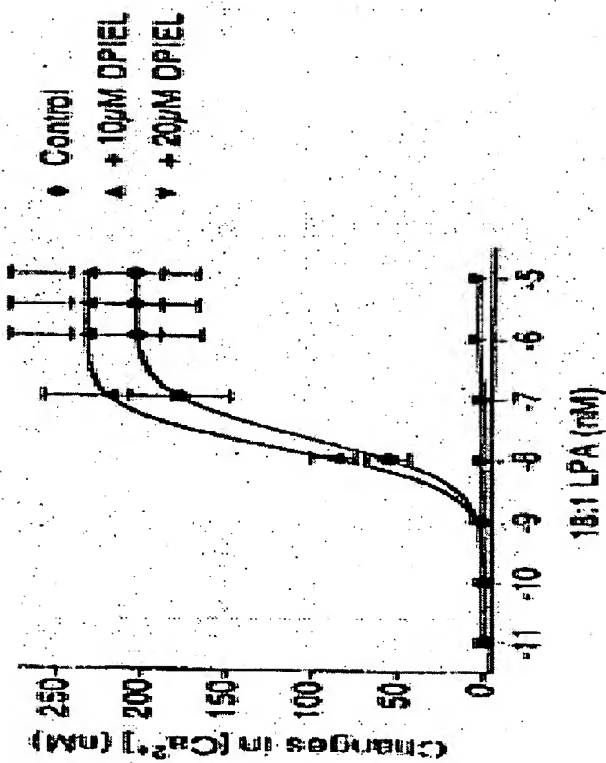
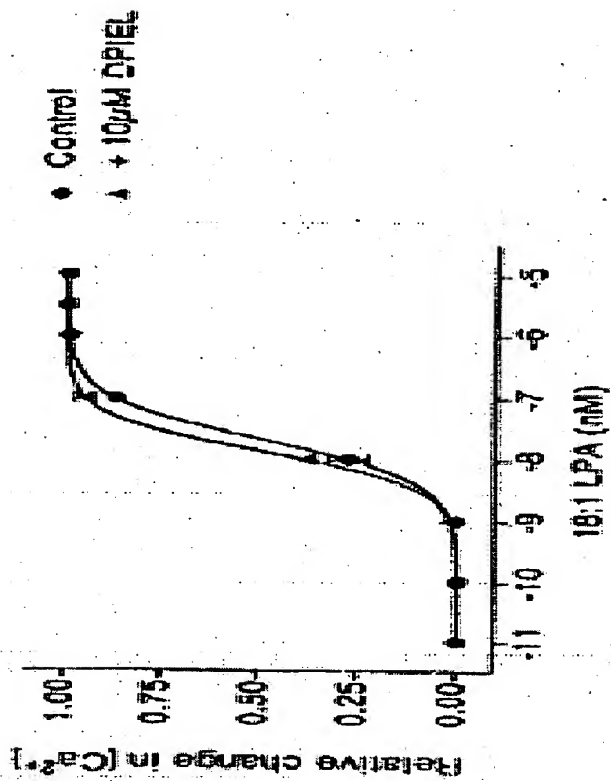


Figure 6

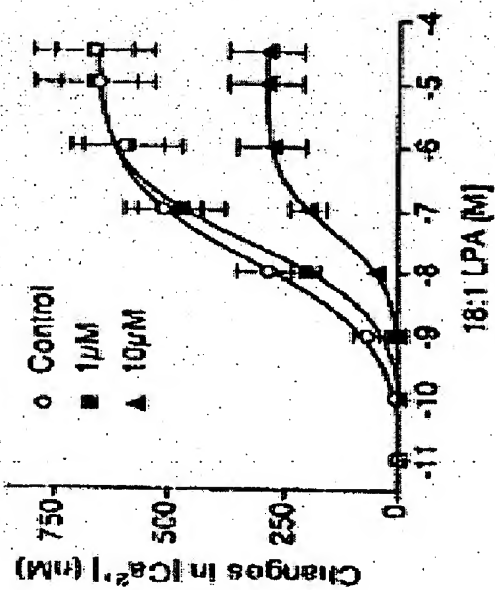
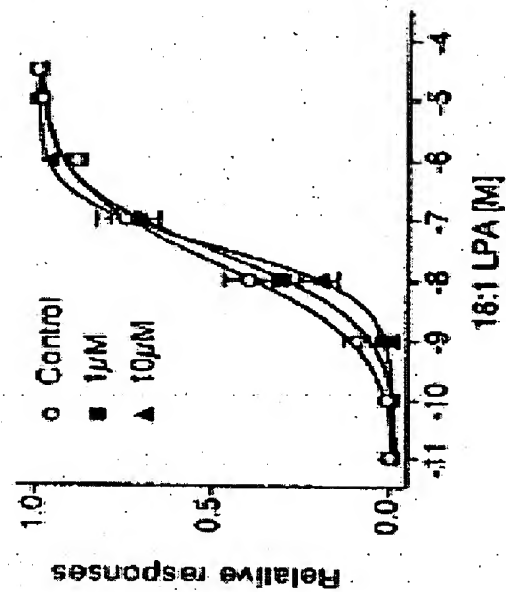


Figure 7

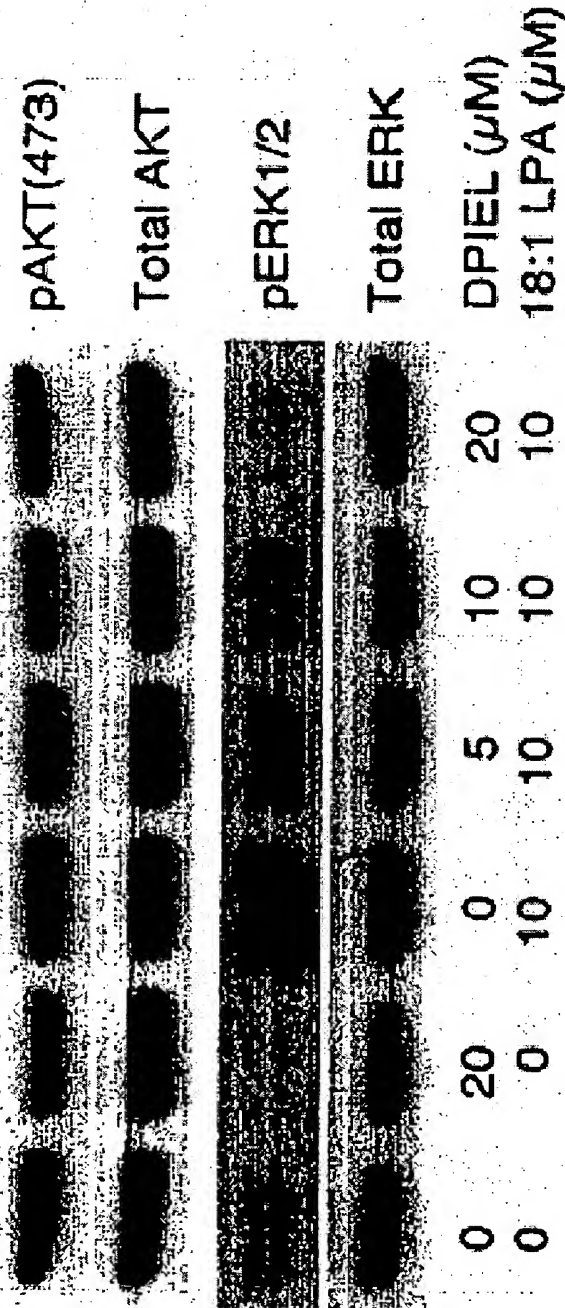
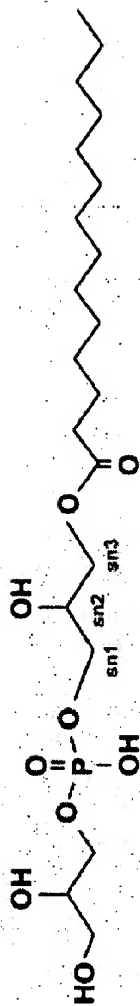
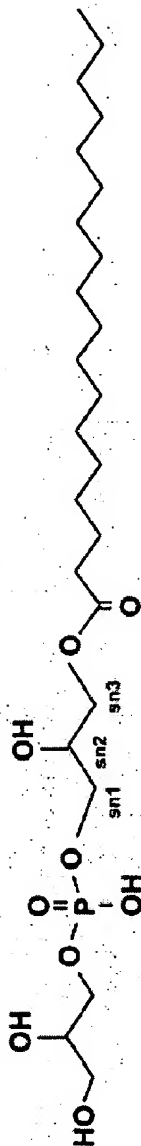


Figure 8

14:0 LPG



18:0 LPG



18:1 LPG

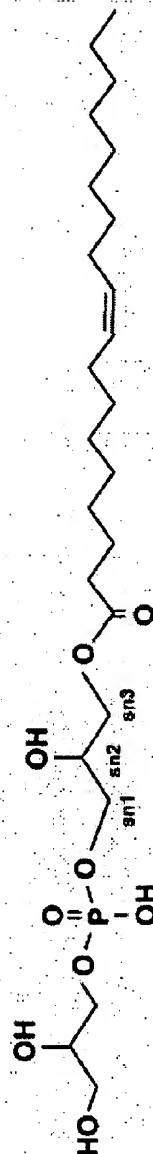


Figure 9

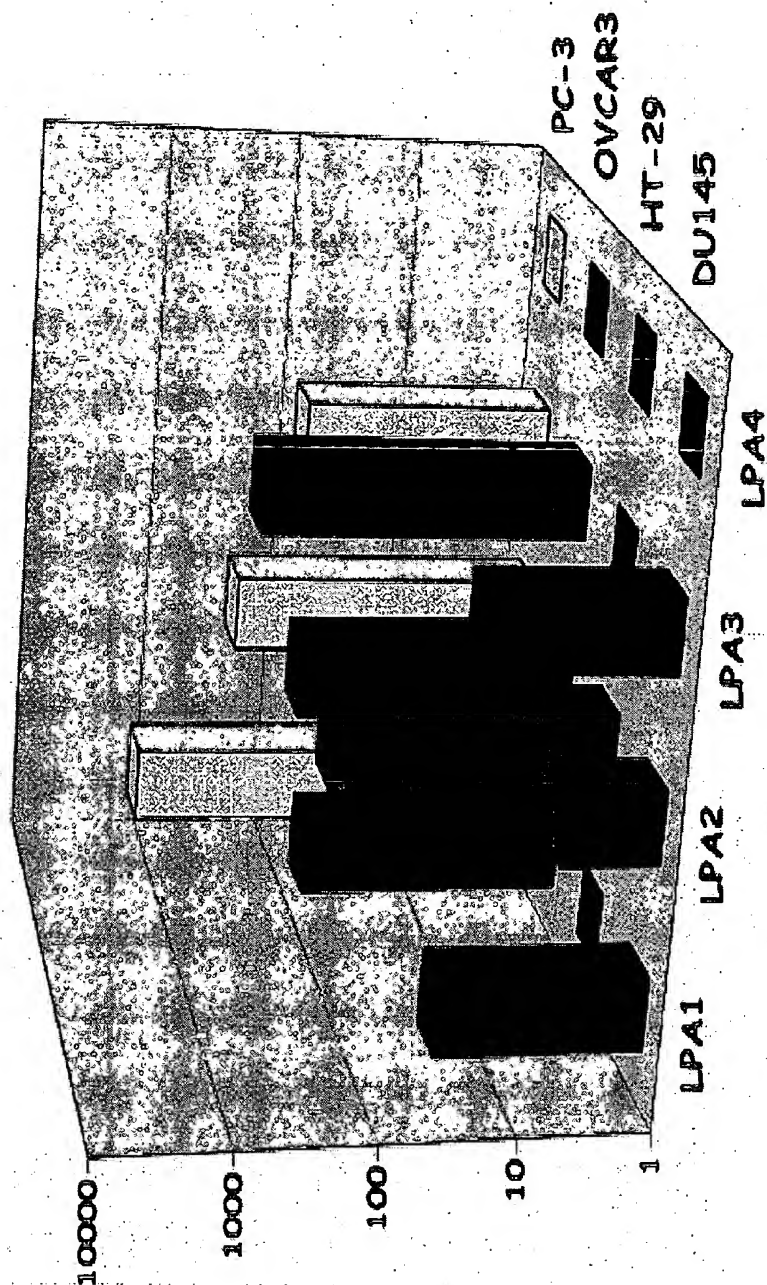


Figure 10

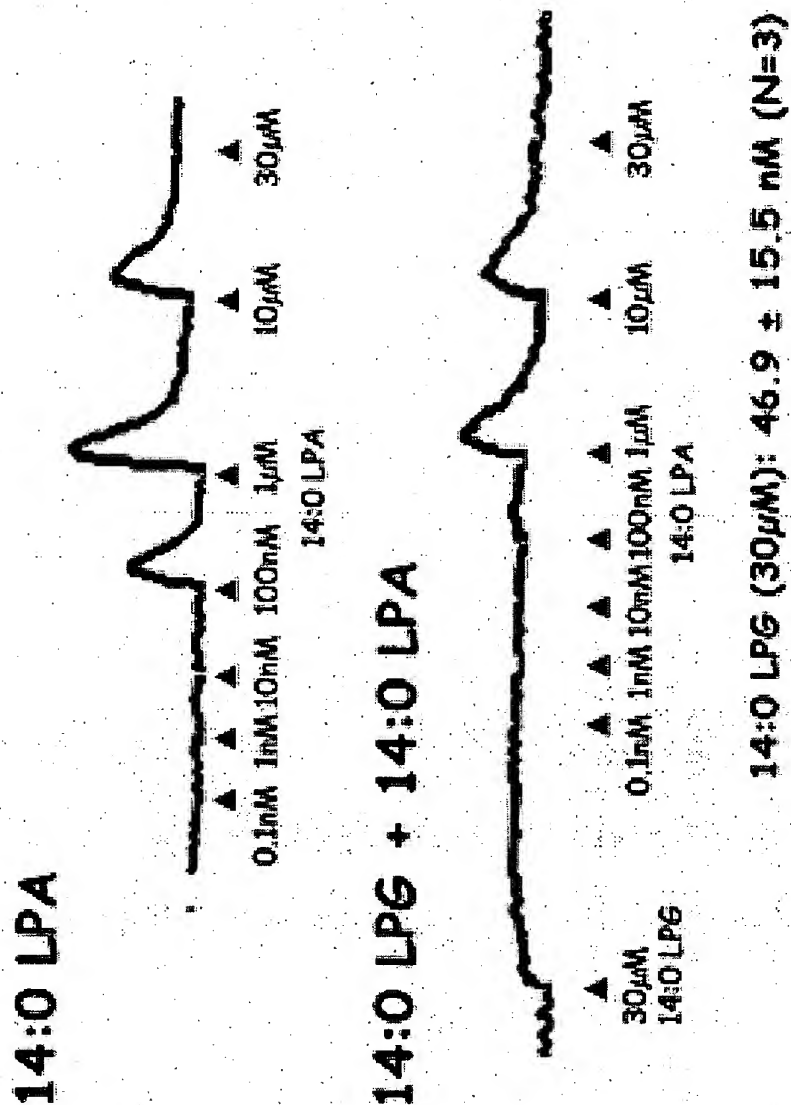


Figure 11

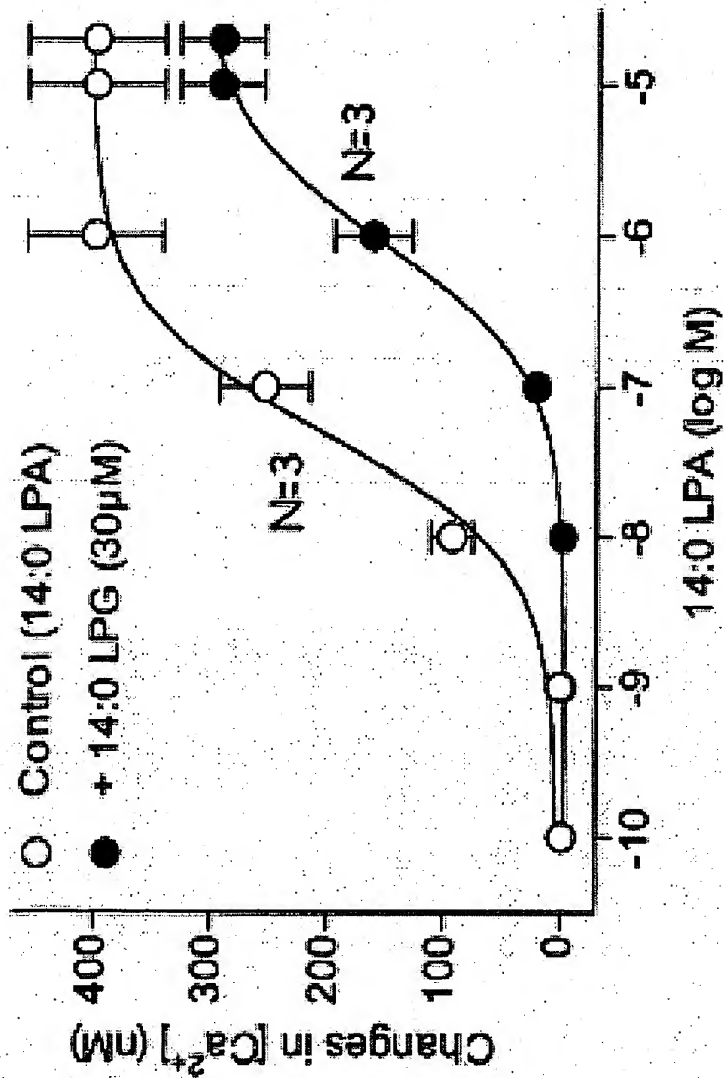


Figure 12

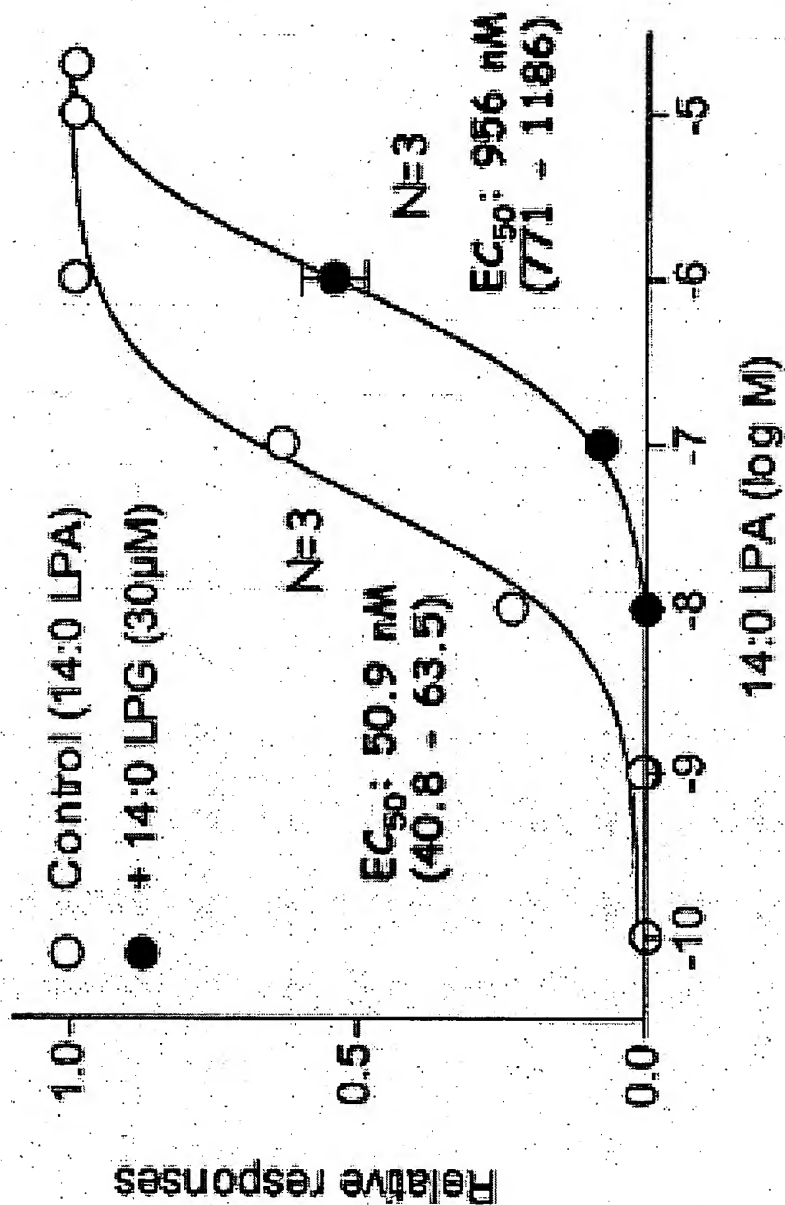


Figure 13

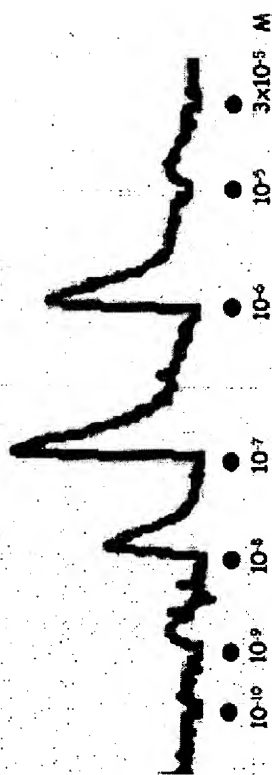


Figure 14

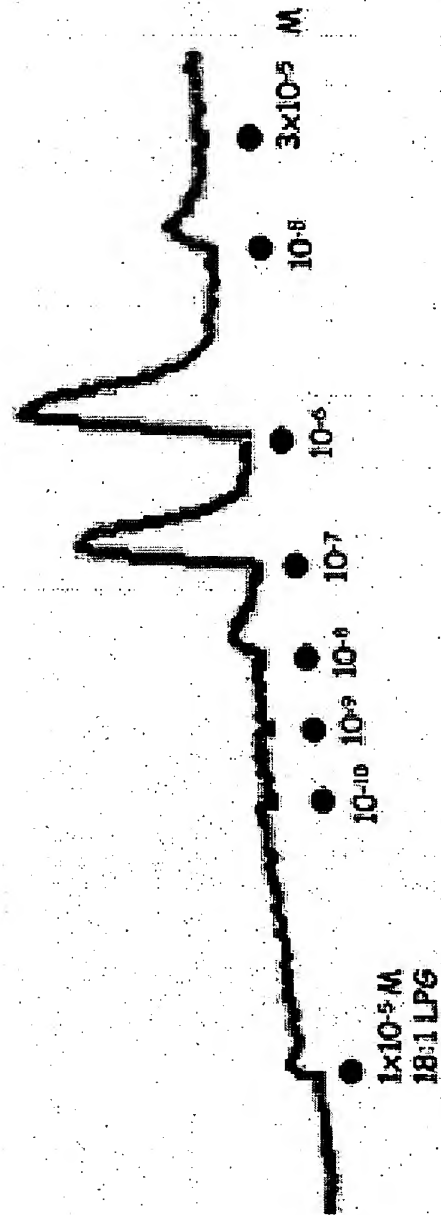


Figure 15

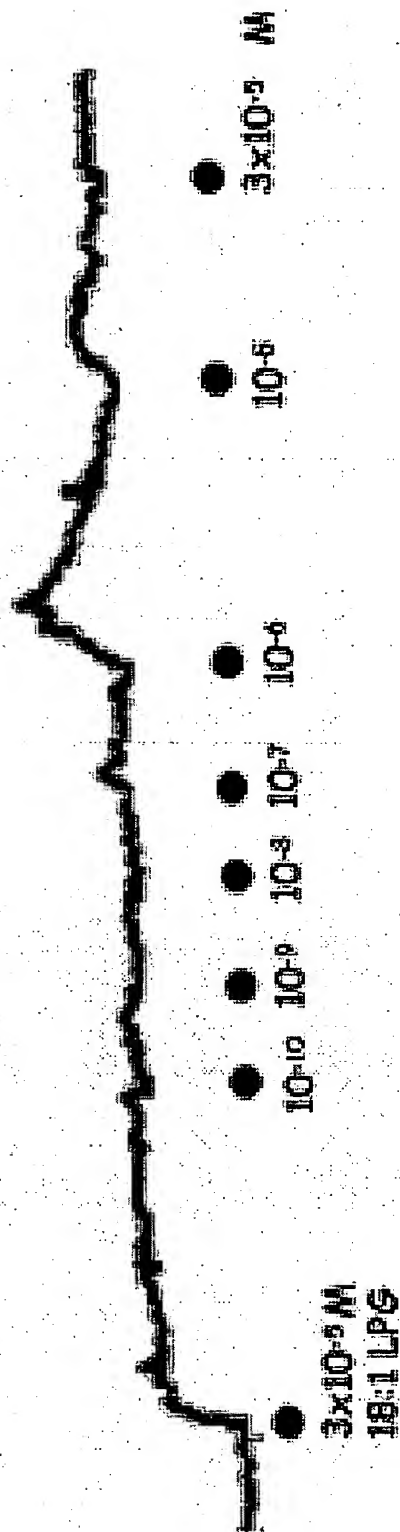


Figure 16

Concentration-dependent inhibition

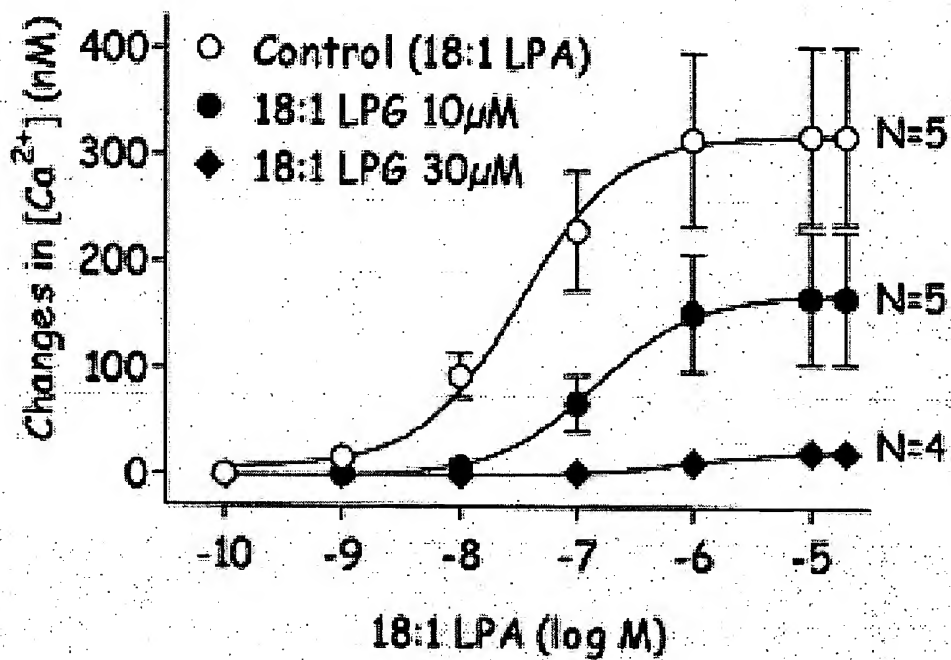


Figure 17

Curve-shift

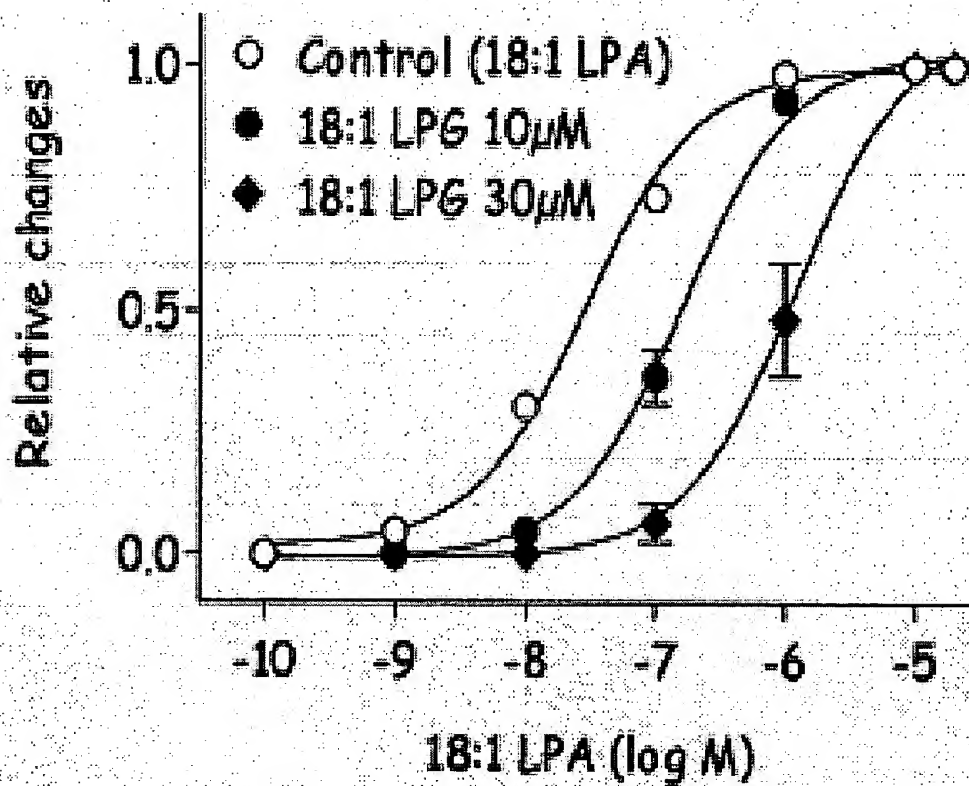


Figure 18

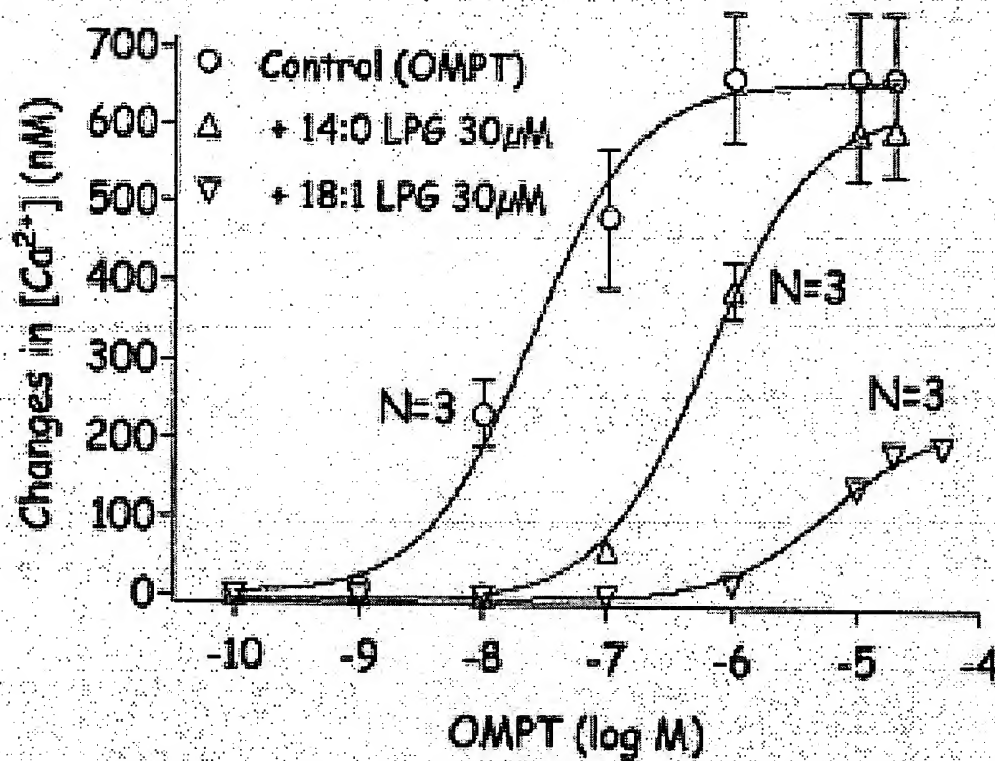


Figure 19

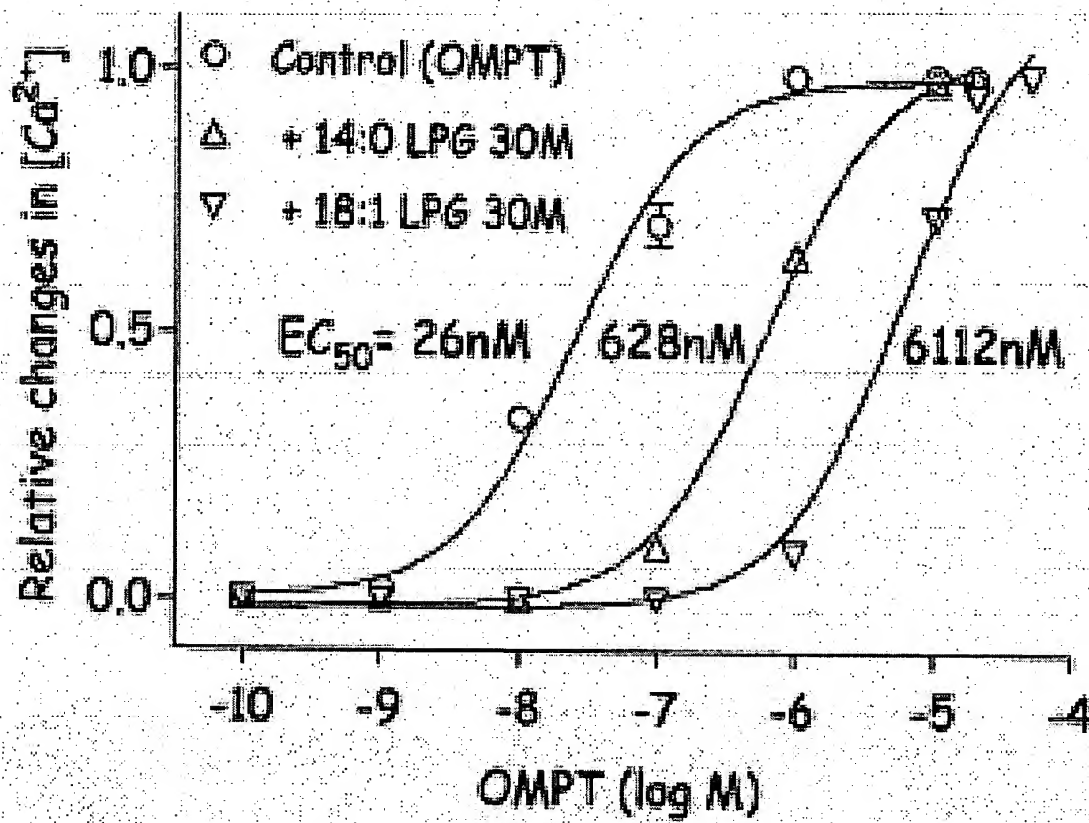


Figure 20

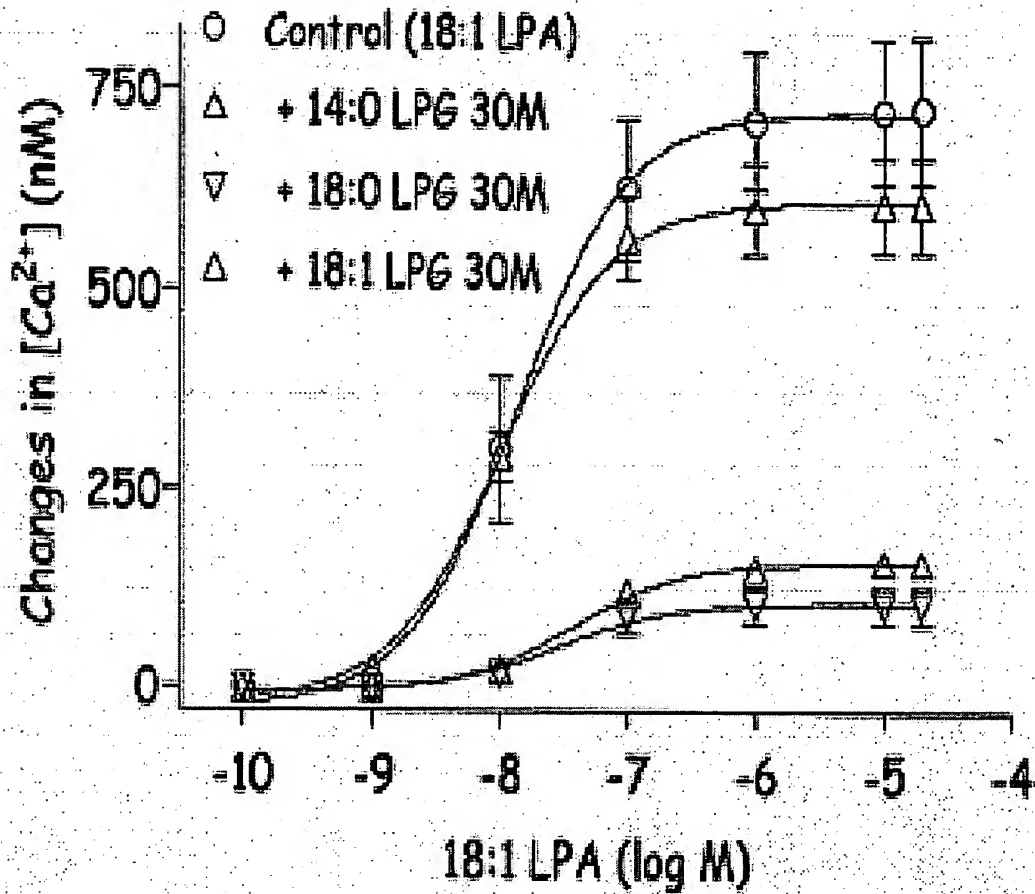


Figure 21

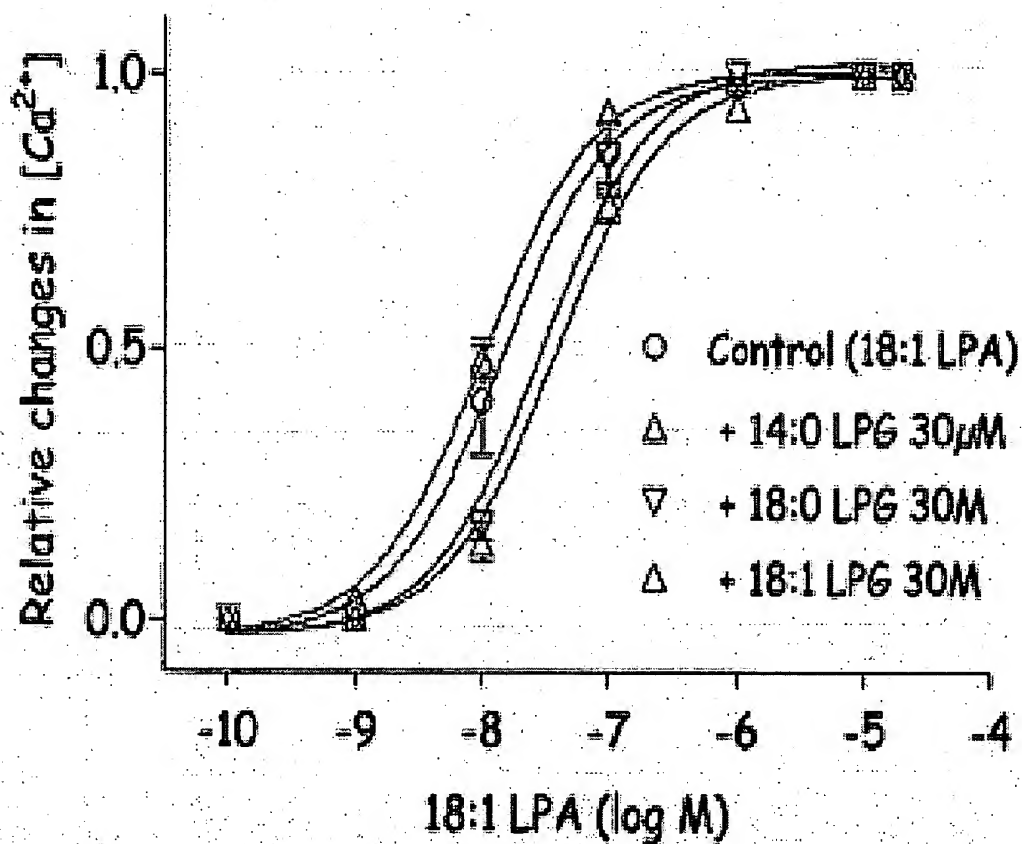


Figure 22

Control (serum-free)

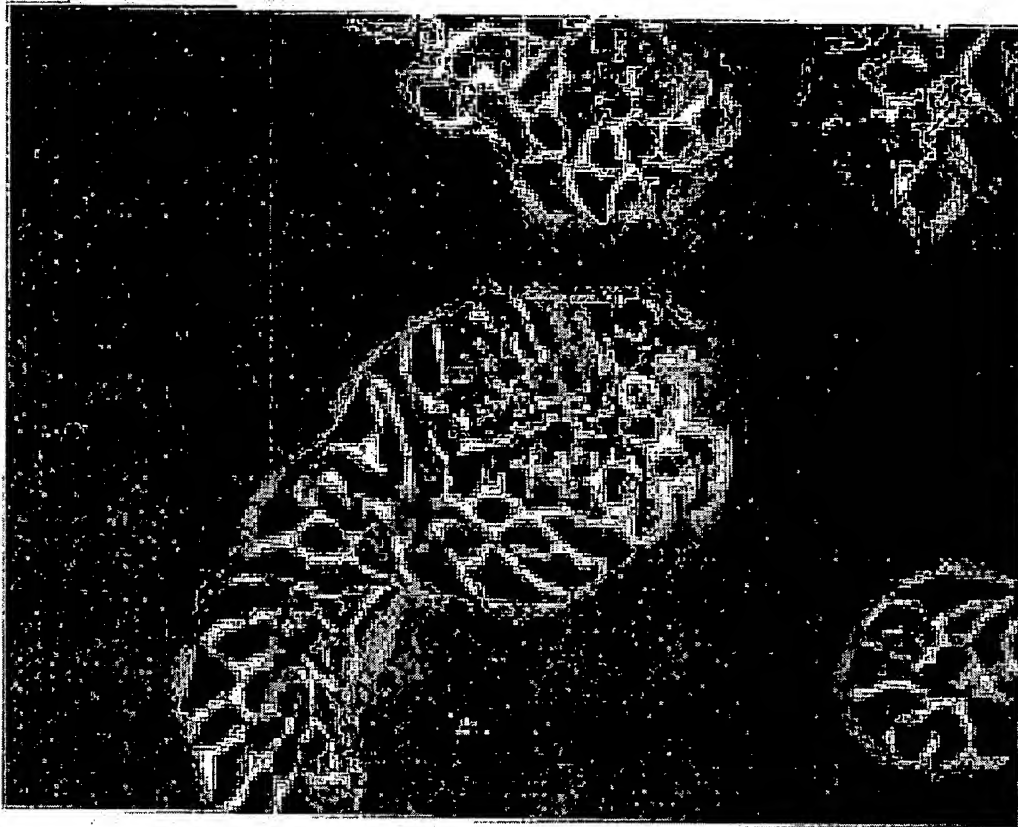


Figure 23

18:0 LPG 10 μ M



Figure 24

18:0 LPG 30 μ M

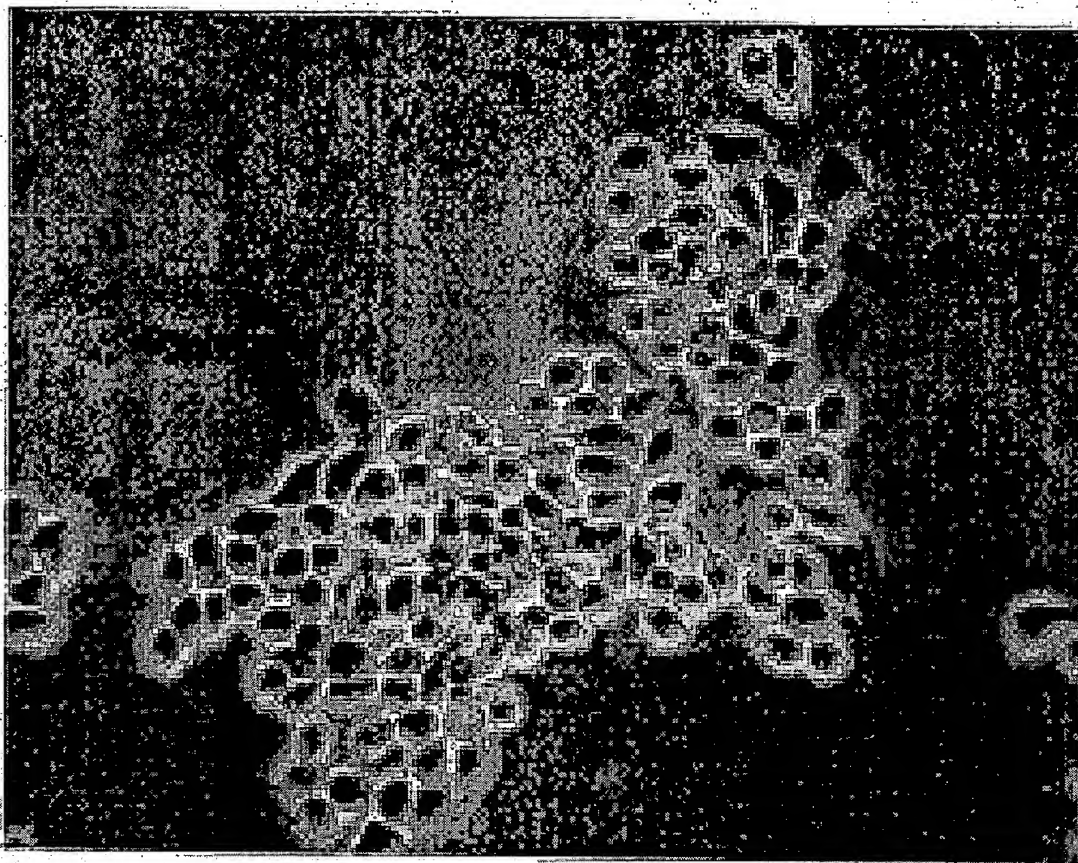


Figure 25

14:0 LPA 10 μ M

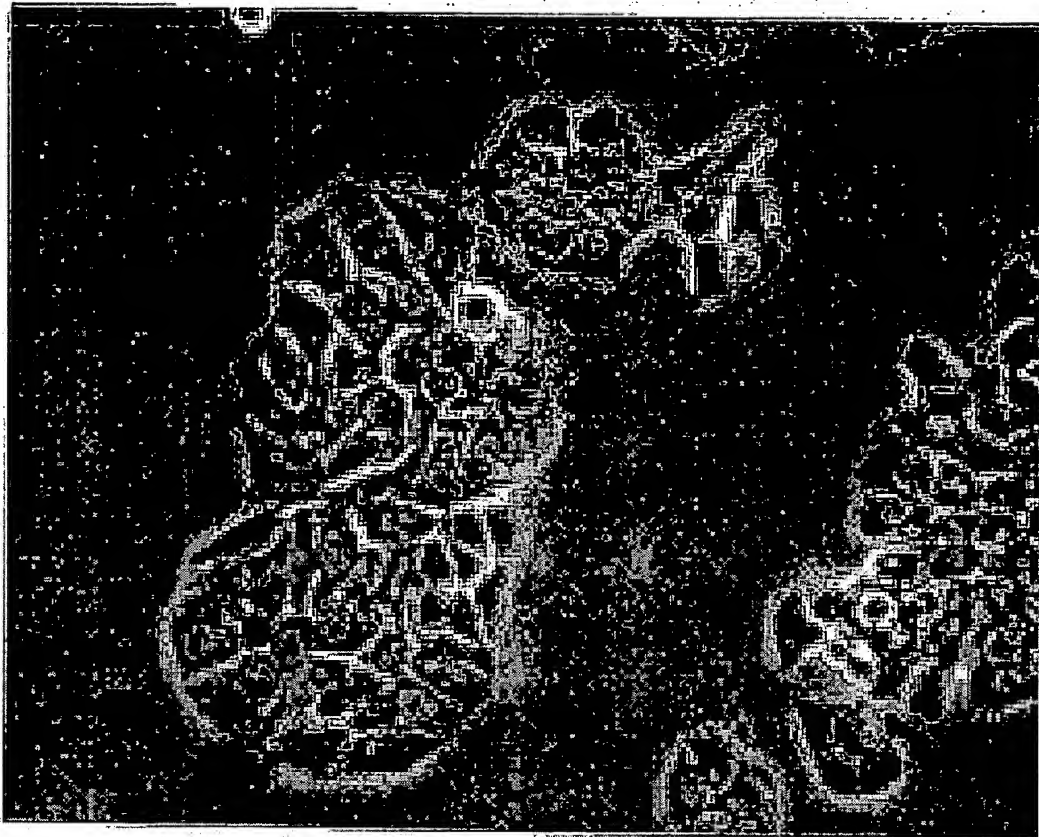


Figure 26

14:0 LPA 10 μ M + 18:0 LPG 10 μ M

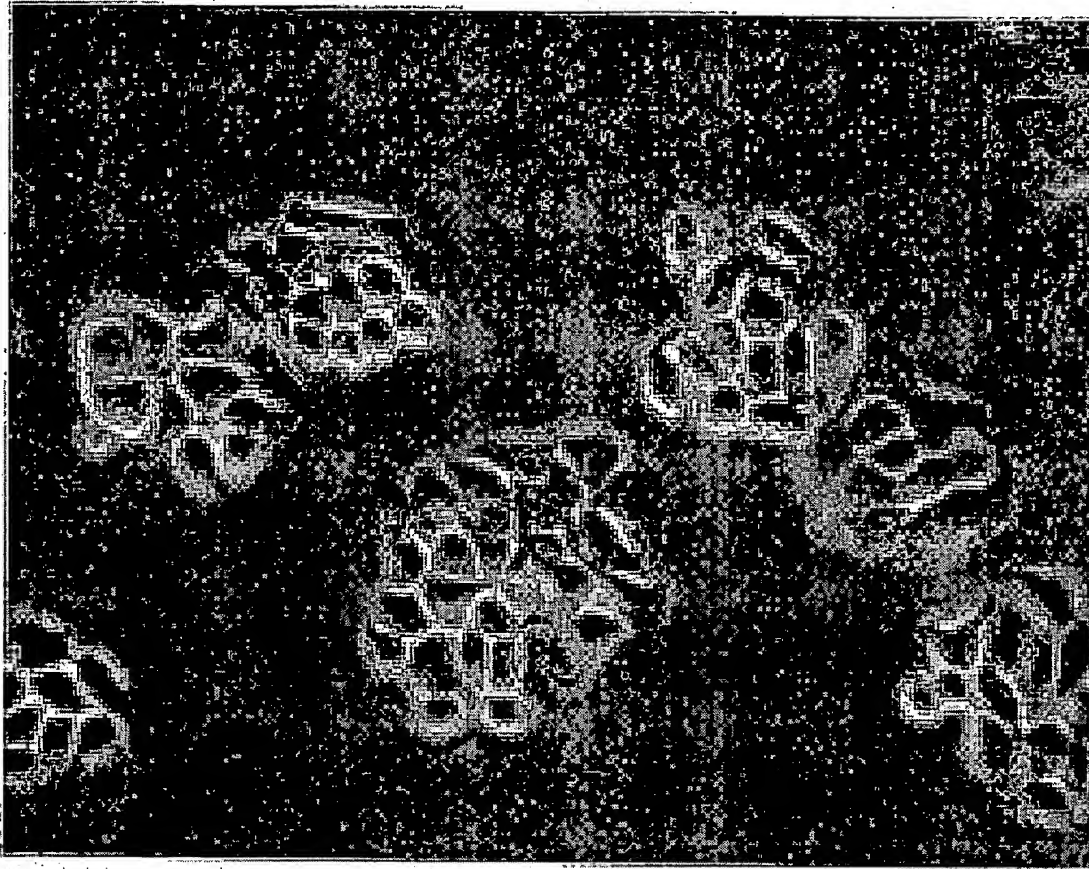


Figure 27

14:0 LPA 10 μ M + 18:0 LPG 30 μ M

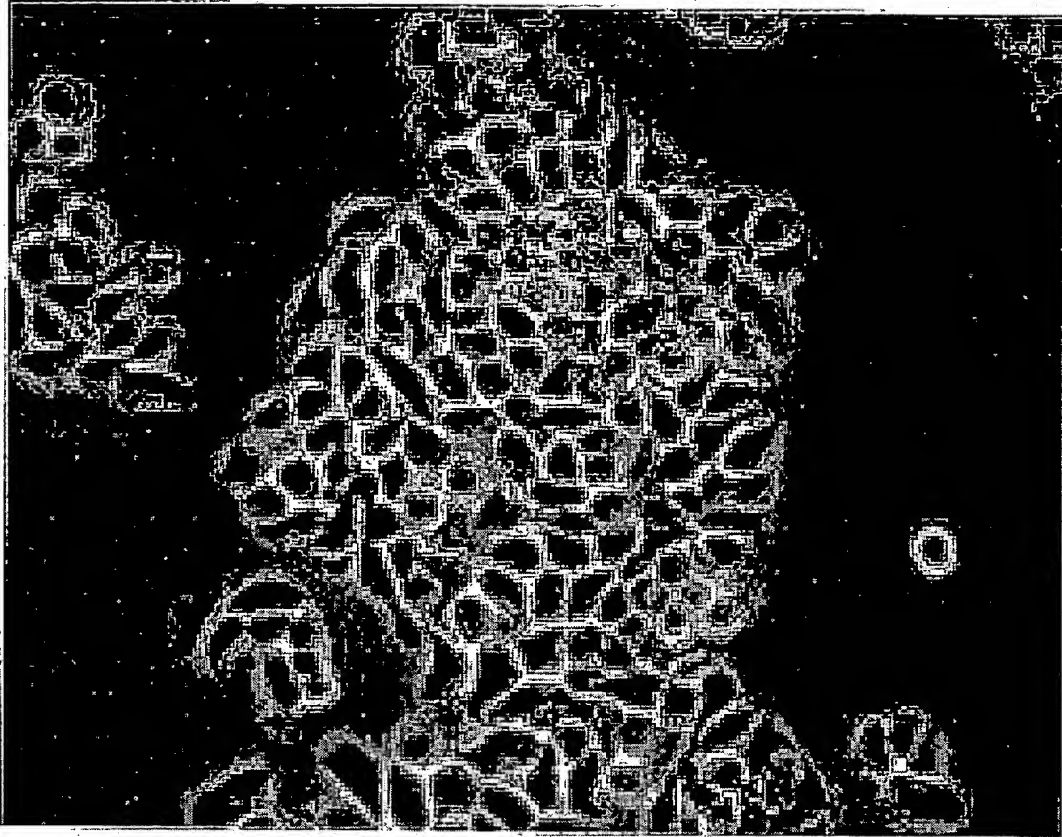


Figure 28

Control

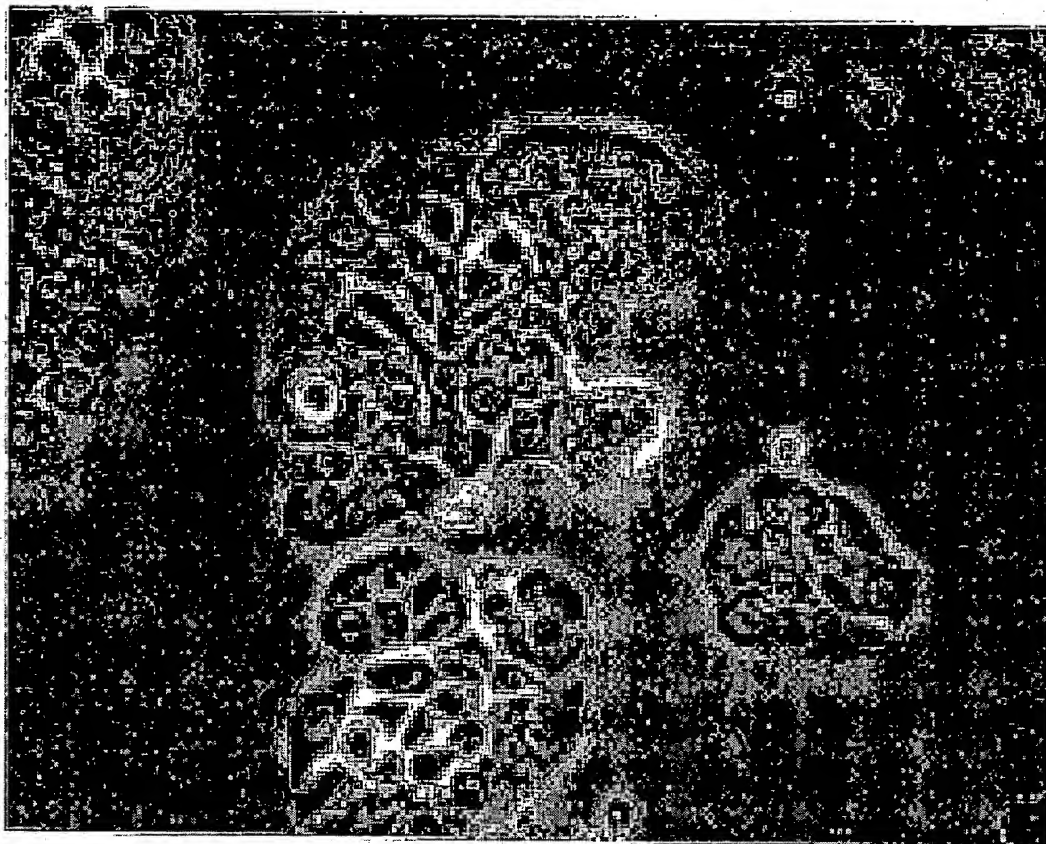


Figure 29

10 μ M 18:0 LPG

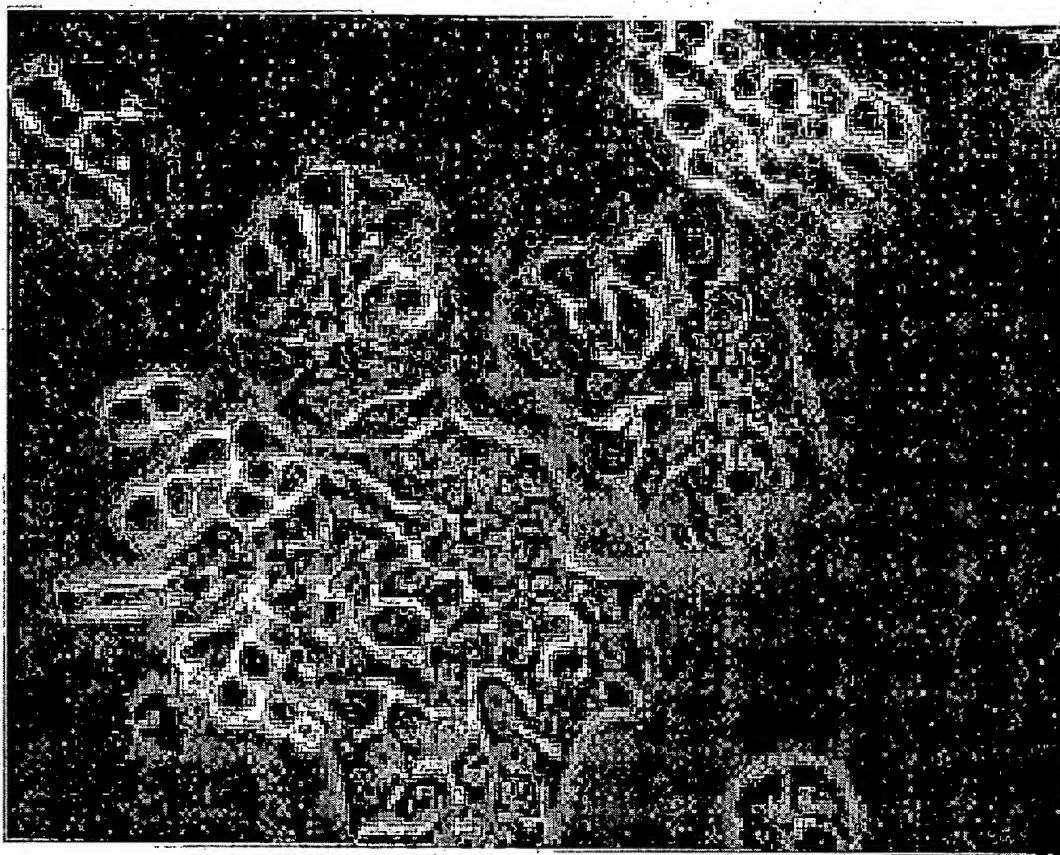


Figure 30

30 μ M 18:0 LPG

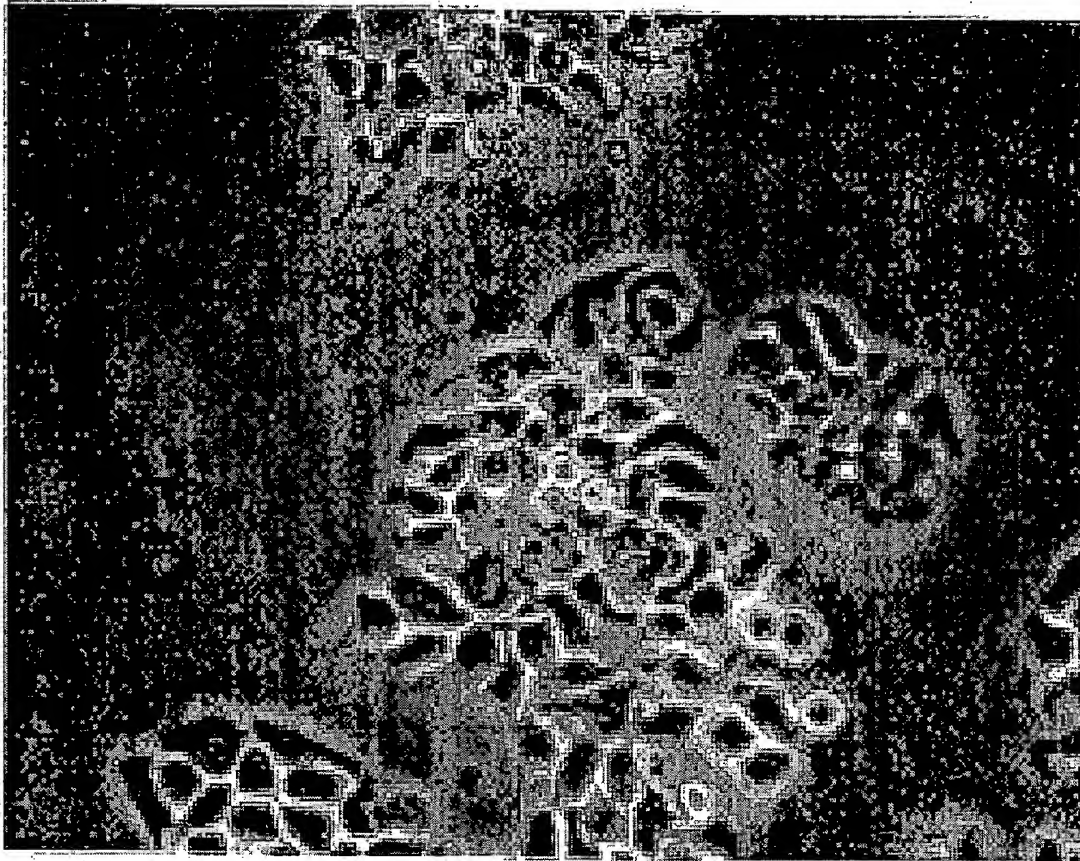


Figure 31

Control

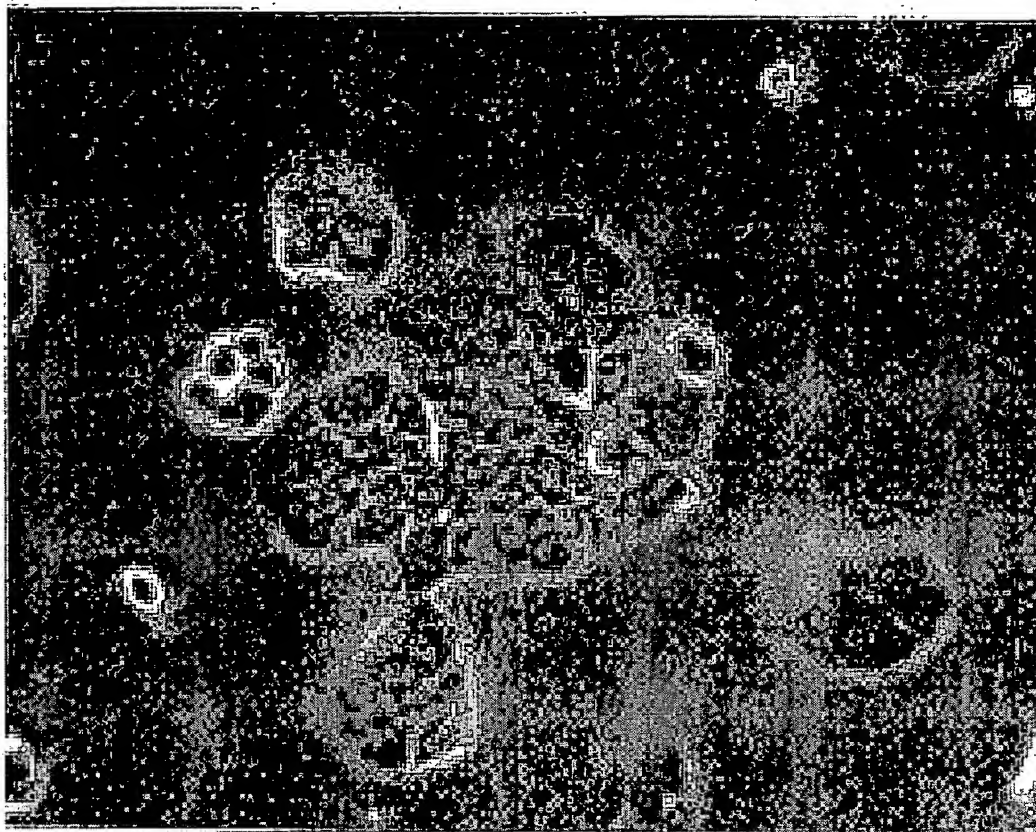


Figure 32

10 μ M 18:0 LPG

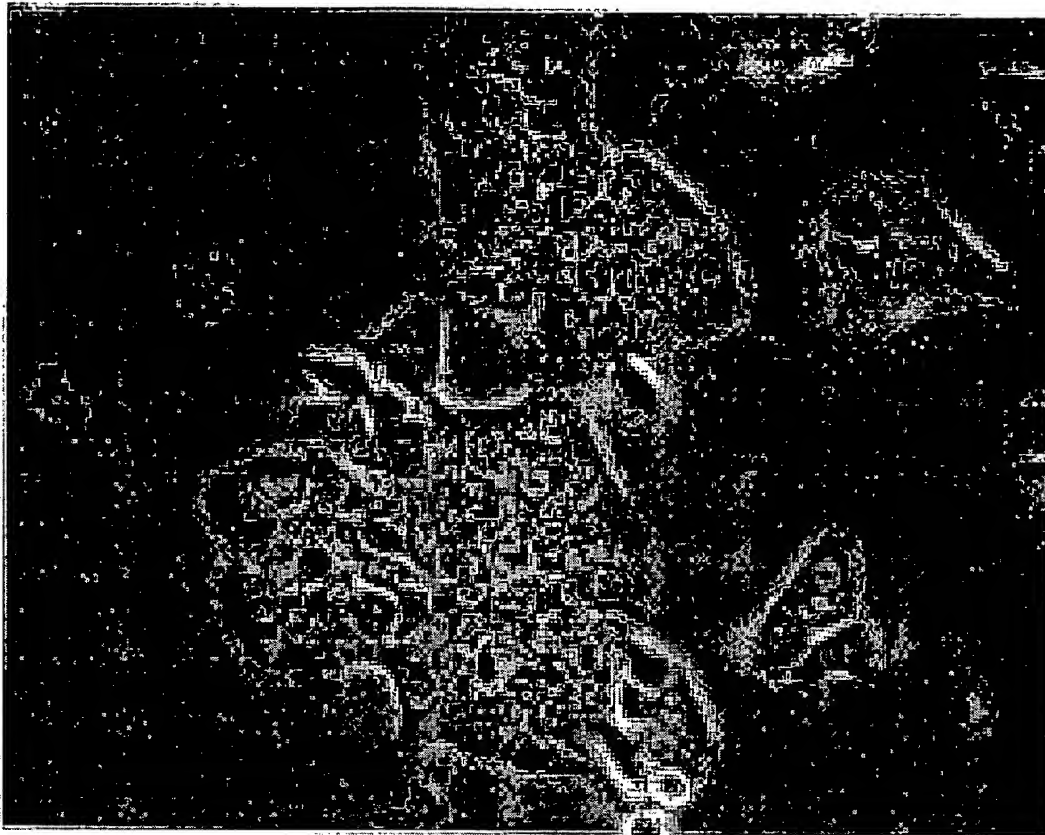


Figure 33

30 μ M 18:0 LPA

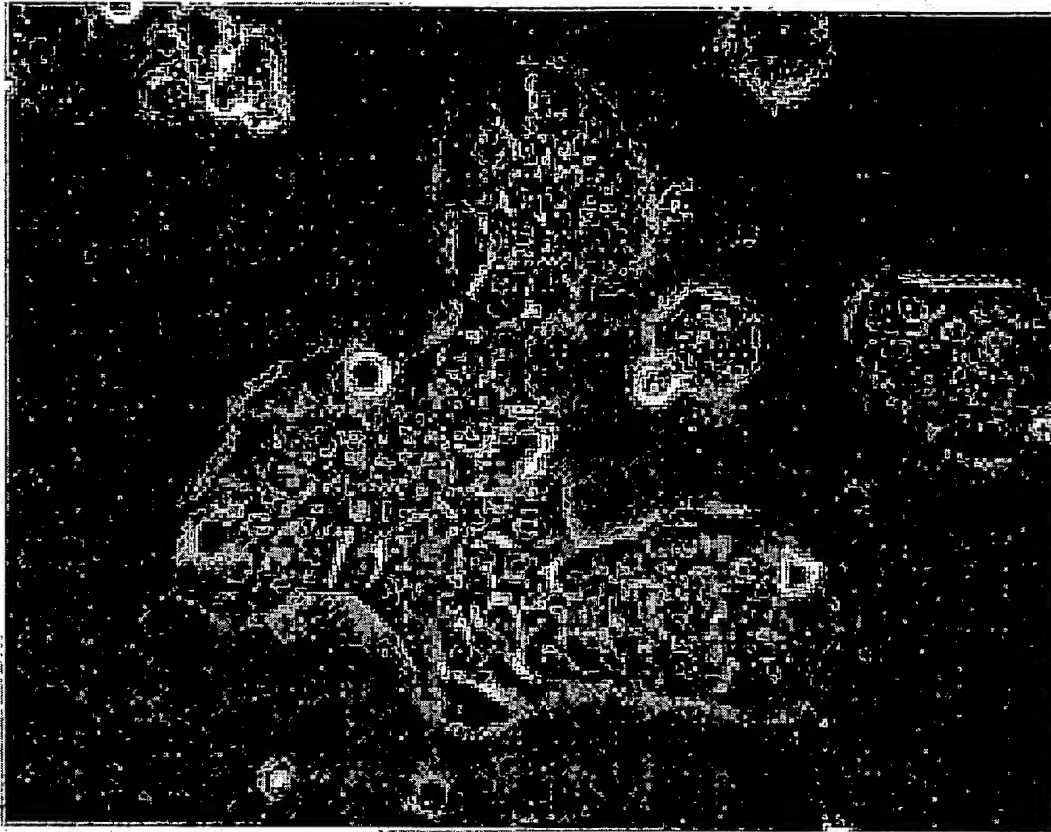


Figure 34

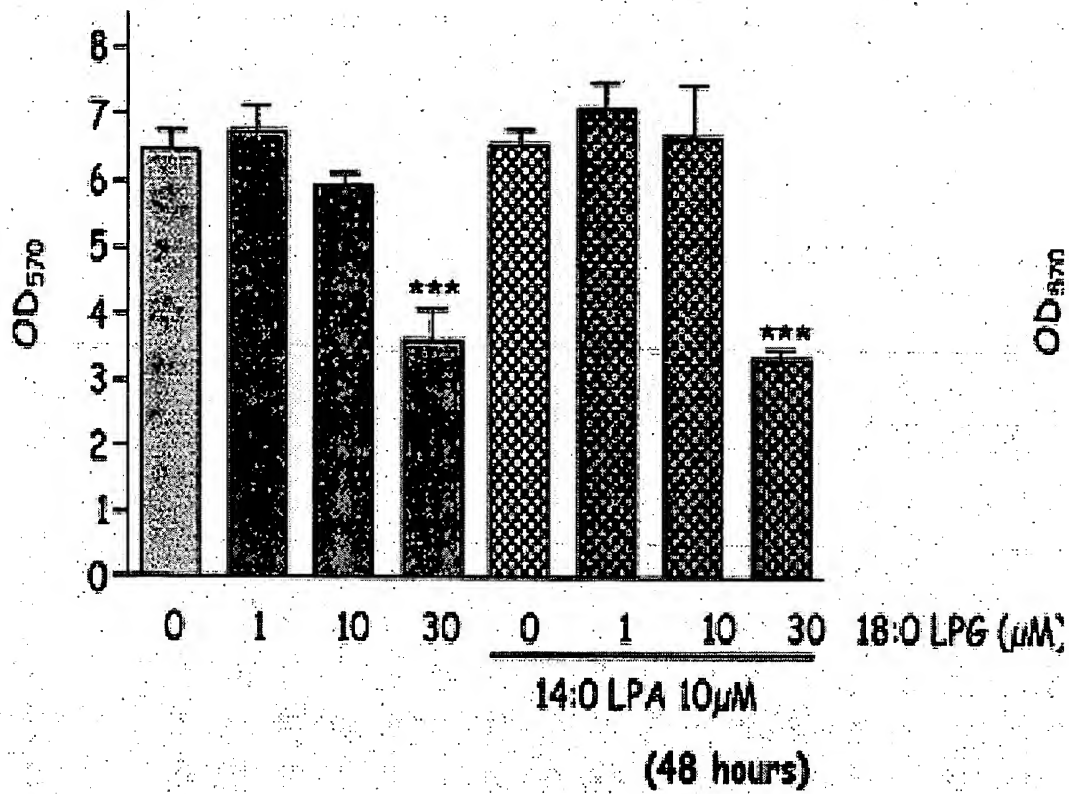


Figure 35

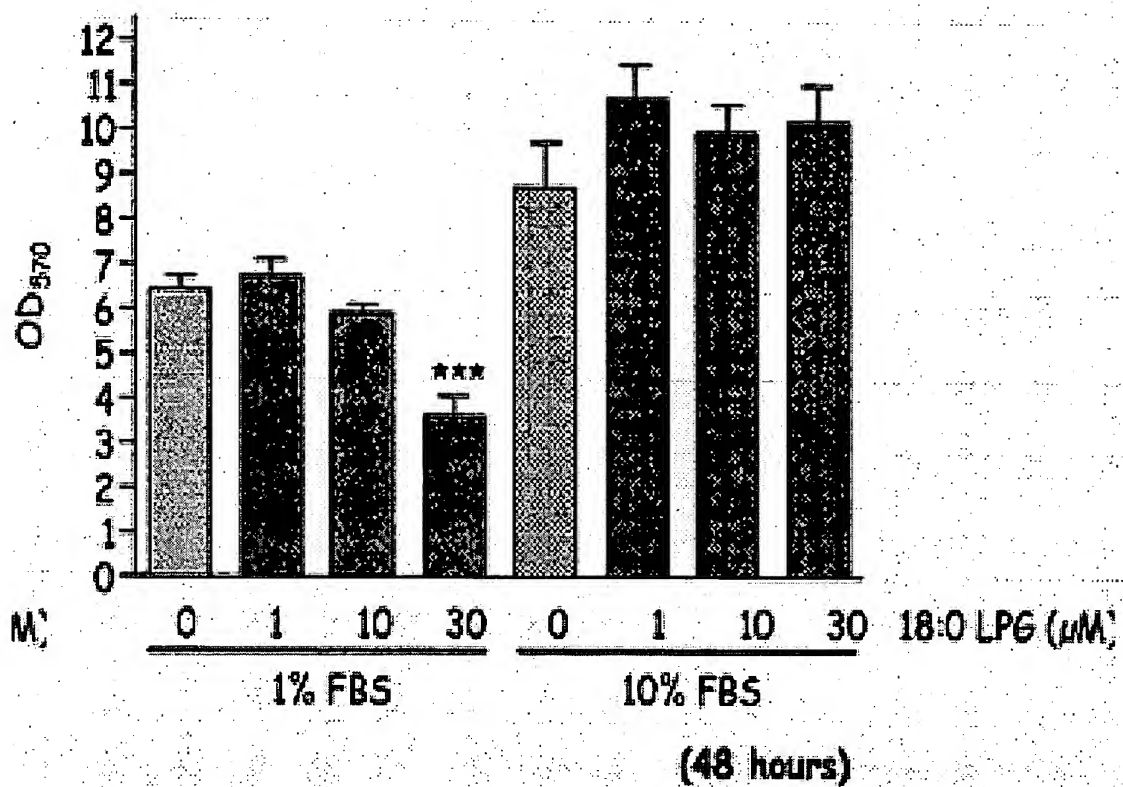


Figure 36

Control (Serum-free)



Figure 37

14:0 LPG (30 μ M) : LPA1 antagonist

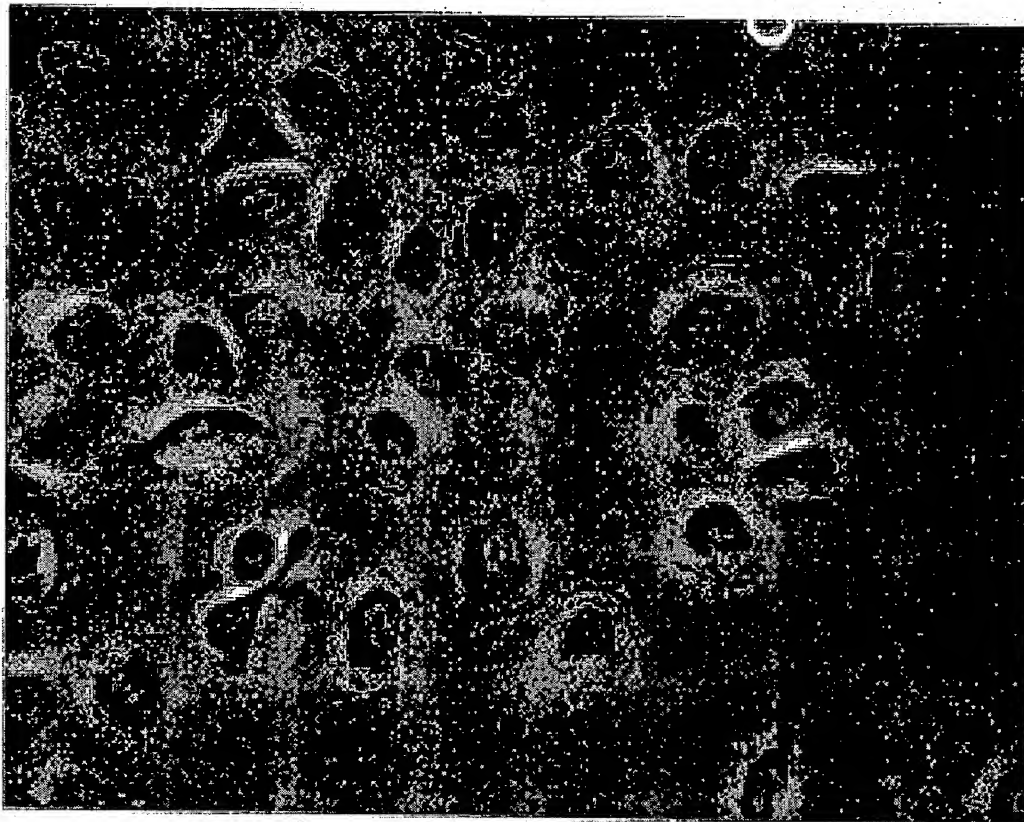


Figure 38

18:0 LPG (30 μ M) : LPA1/2 antagonist

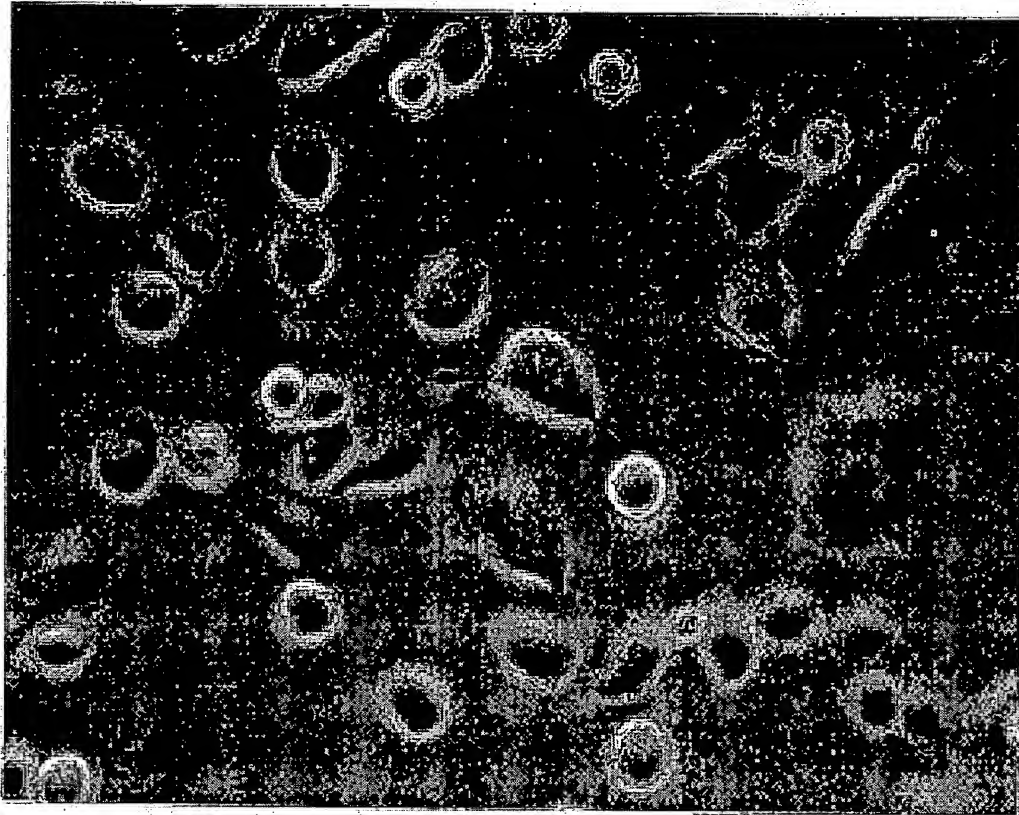


Figure 39

18:1 LPG (30 μ M) : LPA1/2/3 antagonist

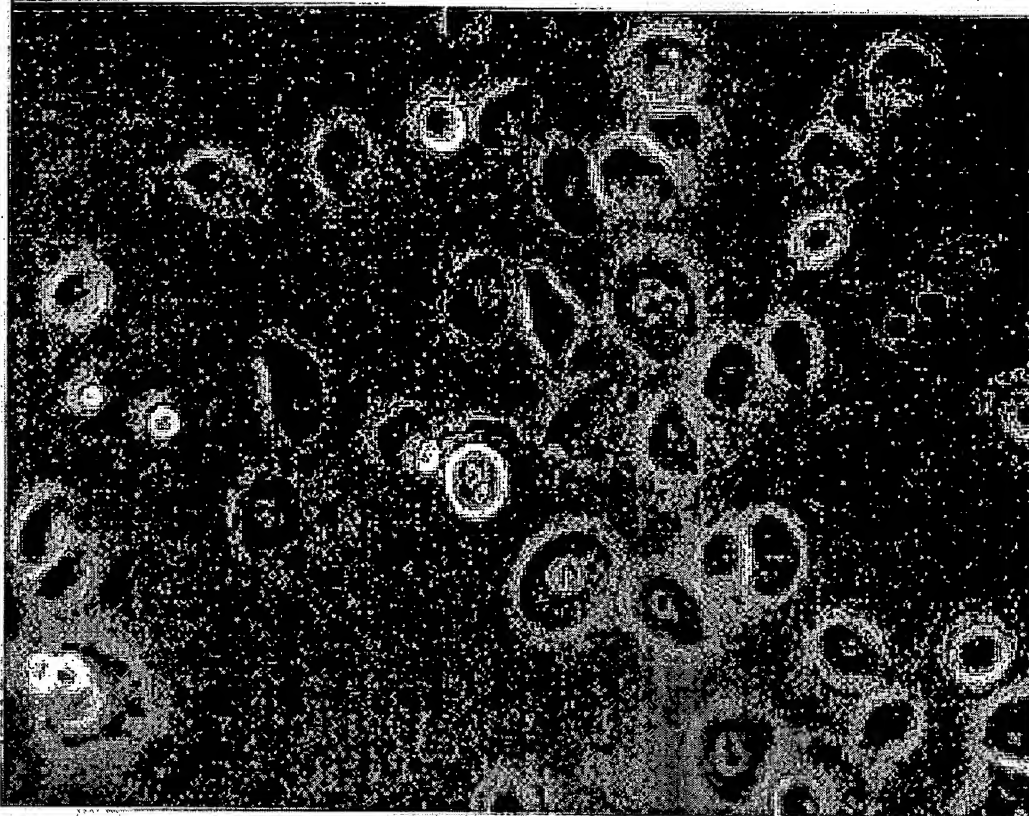


Figure 40

Control (18:1 LPA 10 μ M)

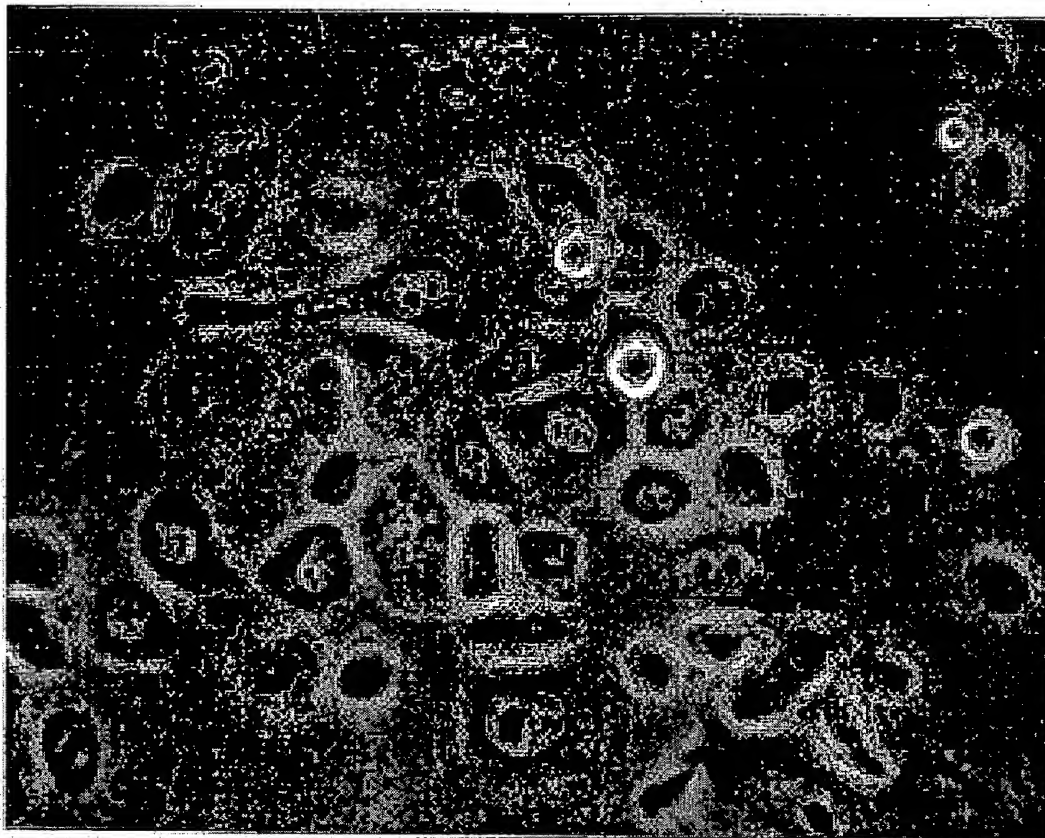


Figure 41

18:1 LPA 10 μ M + 14:0 LP6 (30 μ M)

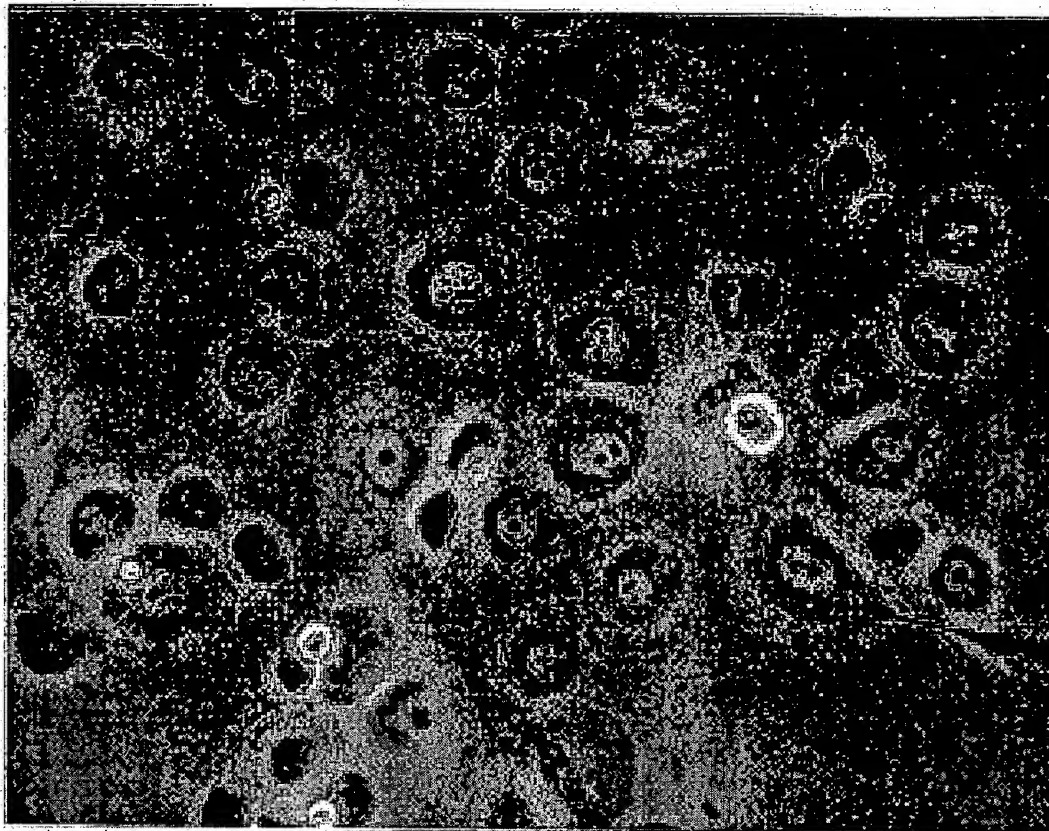


Figure 42

18:1 LPA 10 μ M + 18:0 LPG (30 μ M)

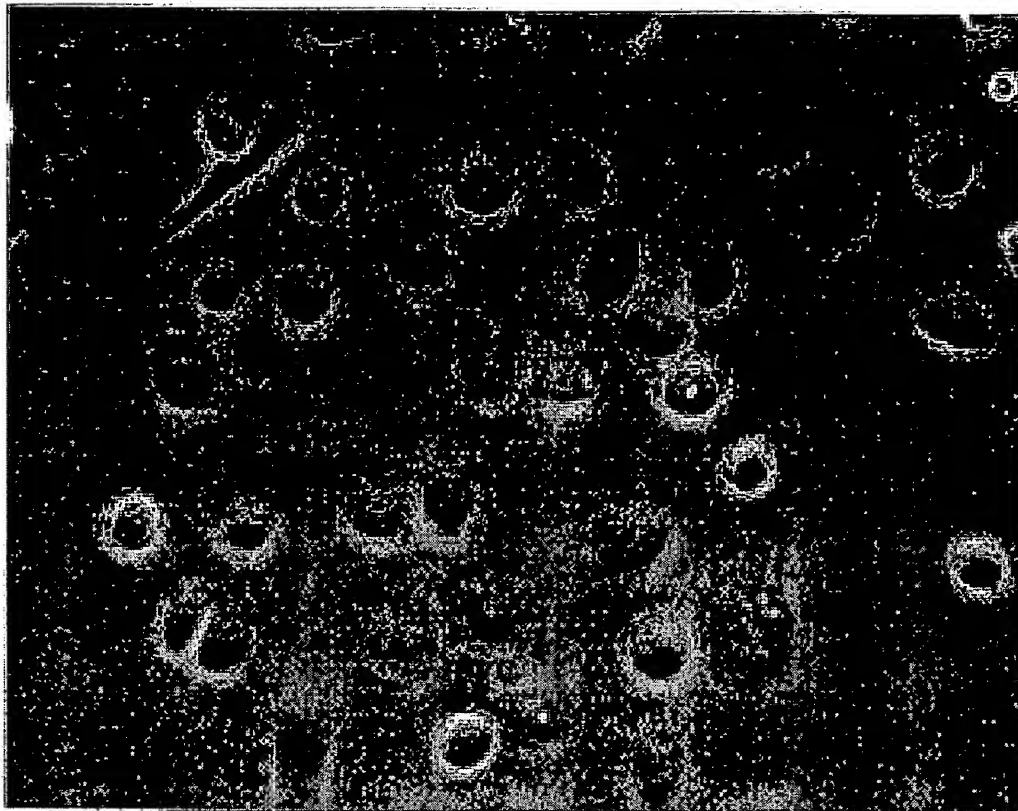


Figure 43

18:1 LPA 10 μ M + 18:1 LPG (30 μ M)

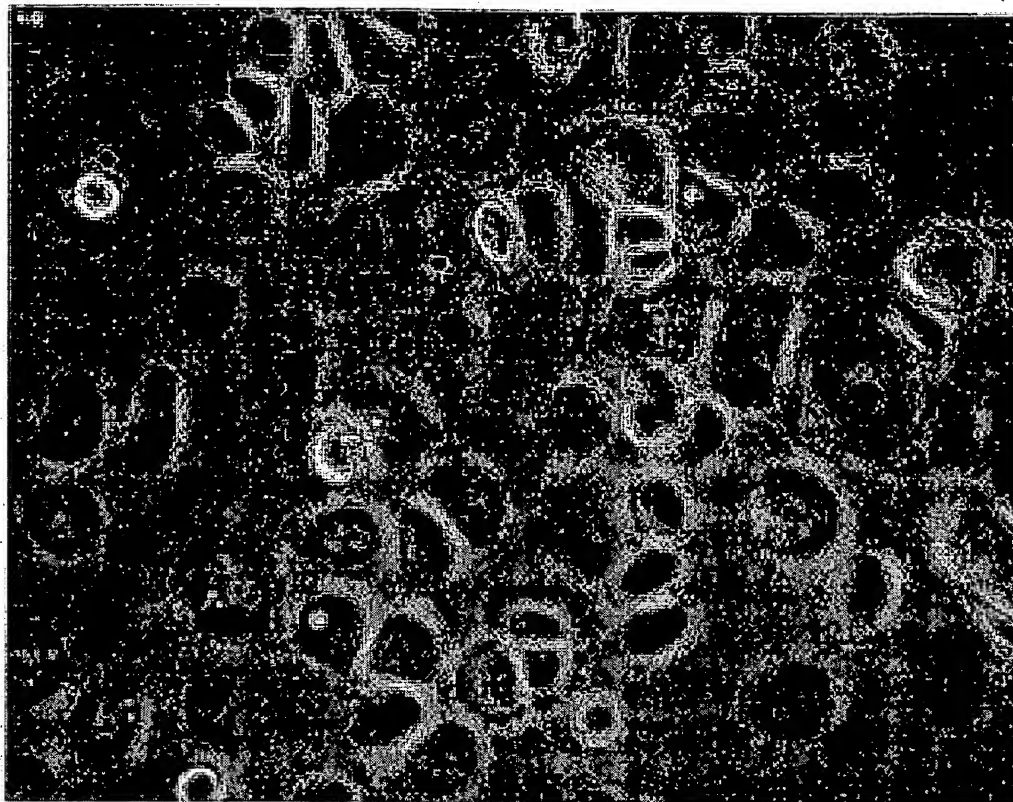


Figure 44

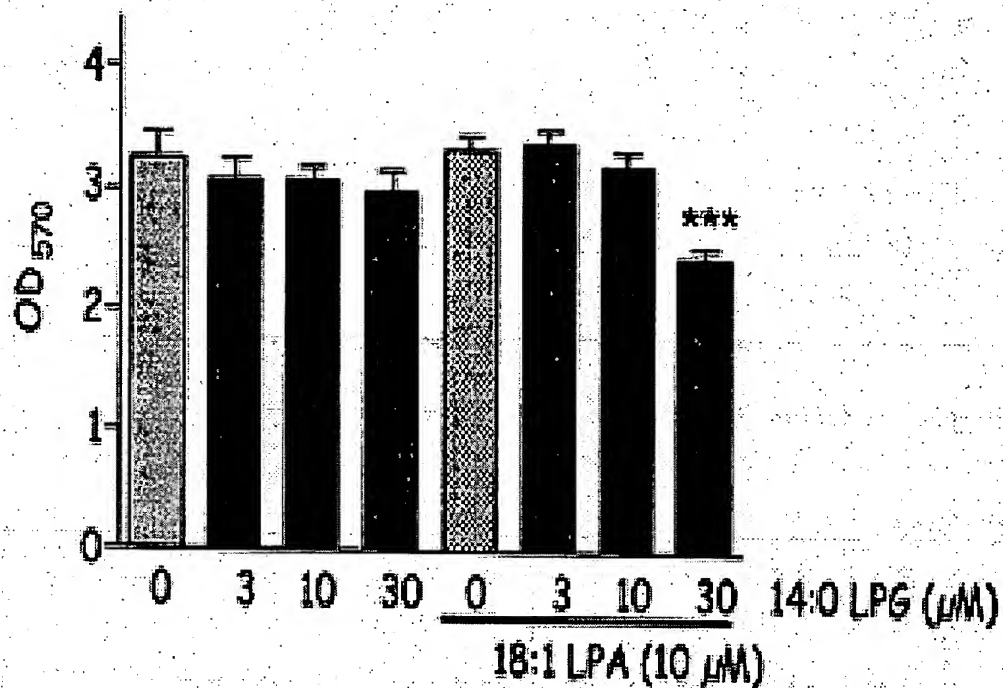


Figure 45

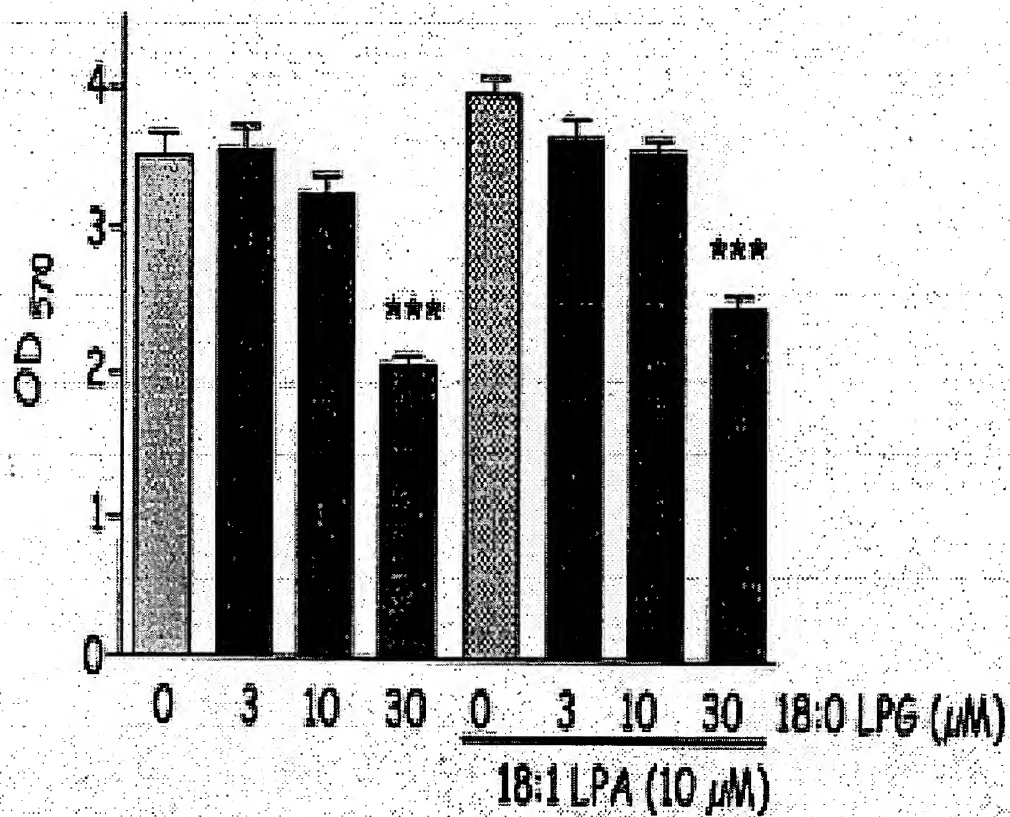


Figure 46

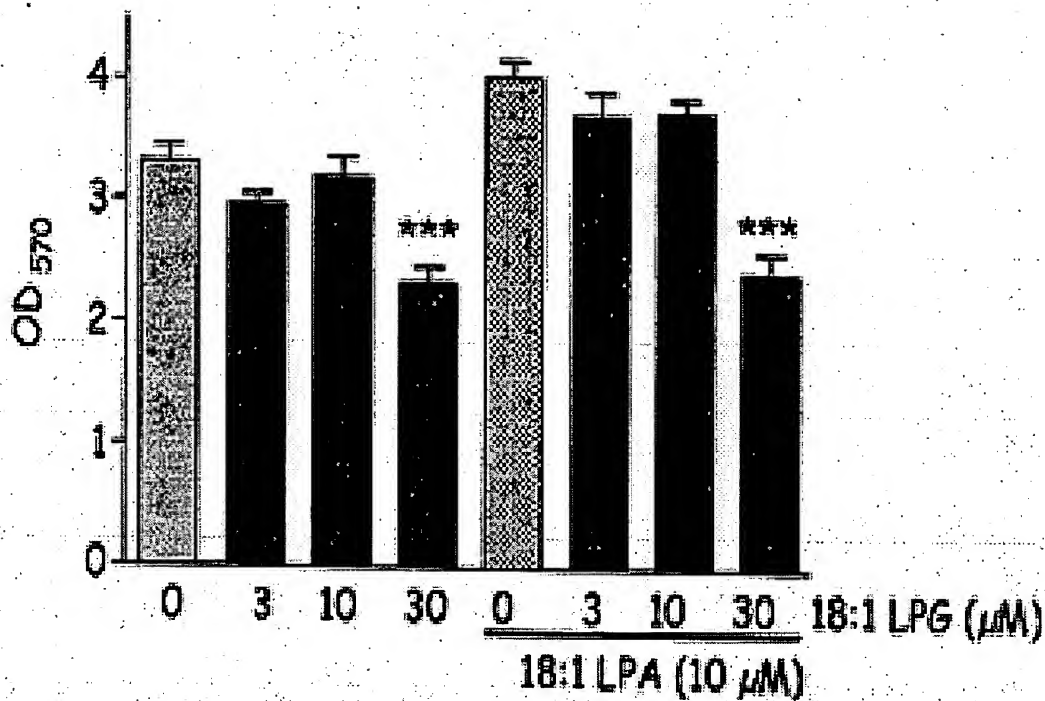


Figure 47

	Inhibition (%)	
	Without LPA	With LPA
14:0 LPG (30 μ M)	8%	26% ↑
18:0 LPG (30 μ M)	41%	37%
18:1 LPG (30 μ M)	29%	39% ↑

Figure 48

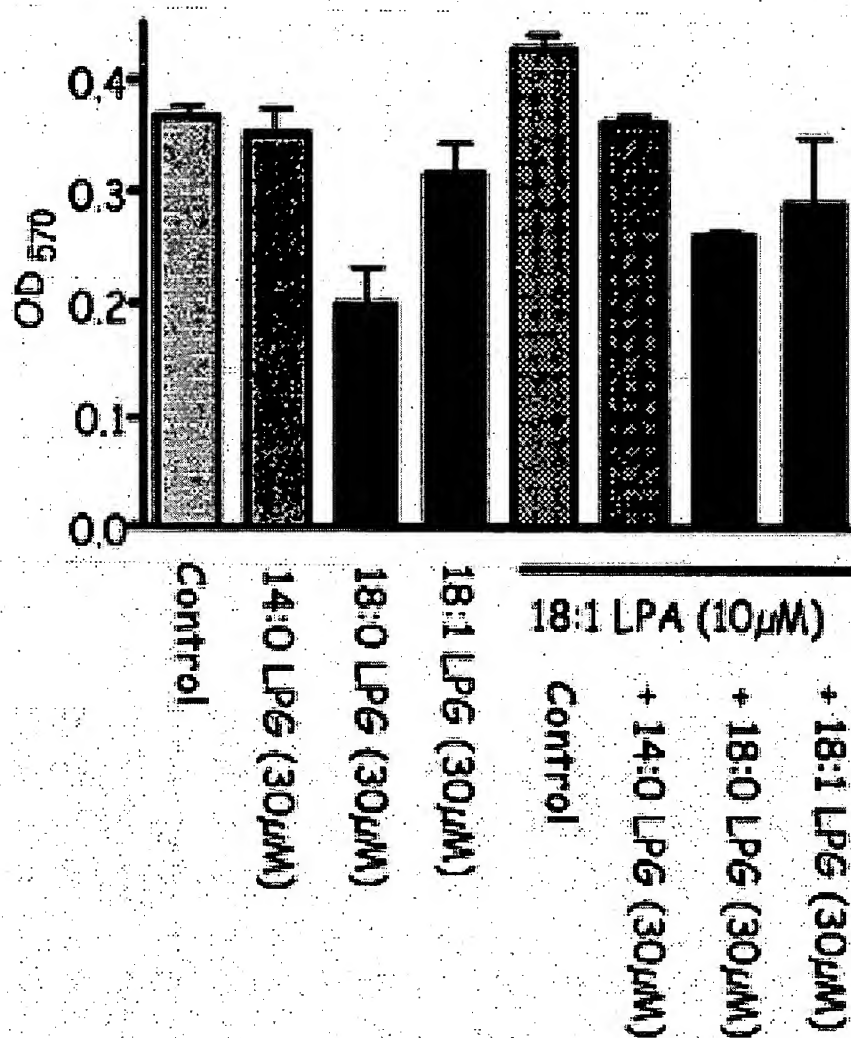


Figure 49

	Inhibition (%)	
	Without LPA	With LPA
14:0 LPG (30 μ M)	4%	16% ↑
18:0 LPG (30 μ M)	46%	49%
18:1 LPG (30 μ M)	13%	32% ↑

Figure 50

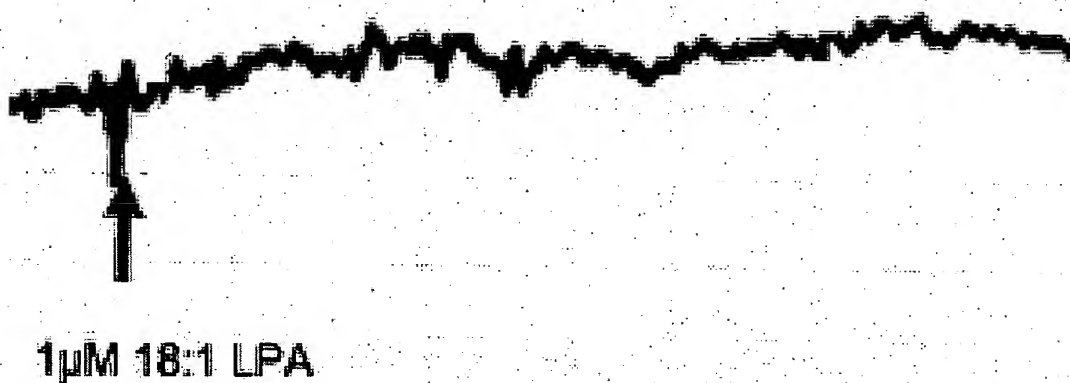


Figure 51



Control

BSA

LPC 10 μ M

EGF 2 μ g/mL

1

10

18:1 LPA (μ M)

Figure 52

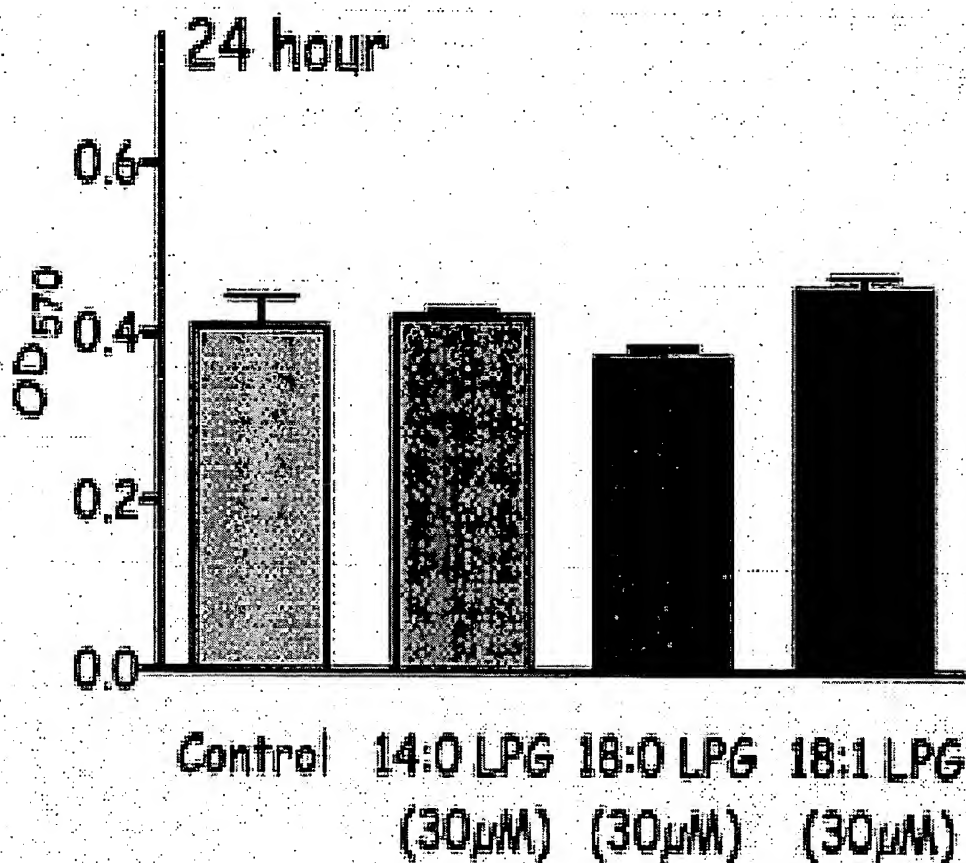


Figure 53

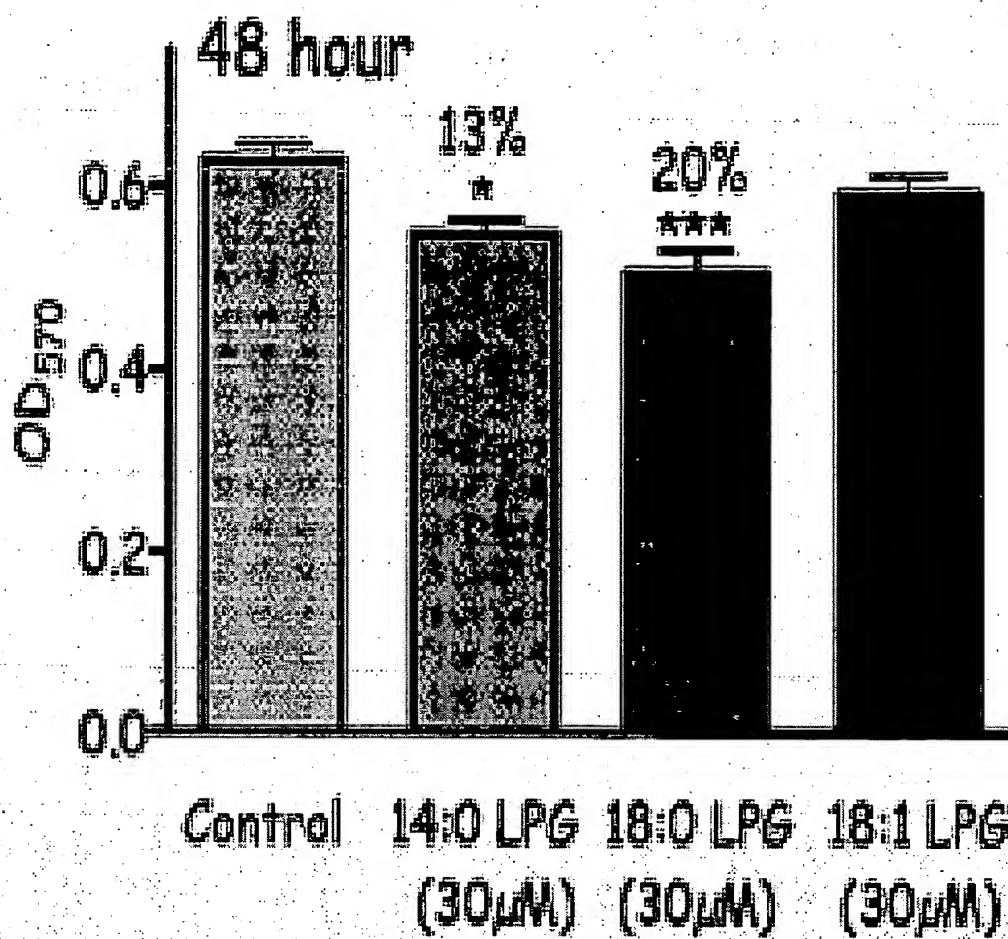


Figure 54

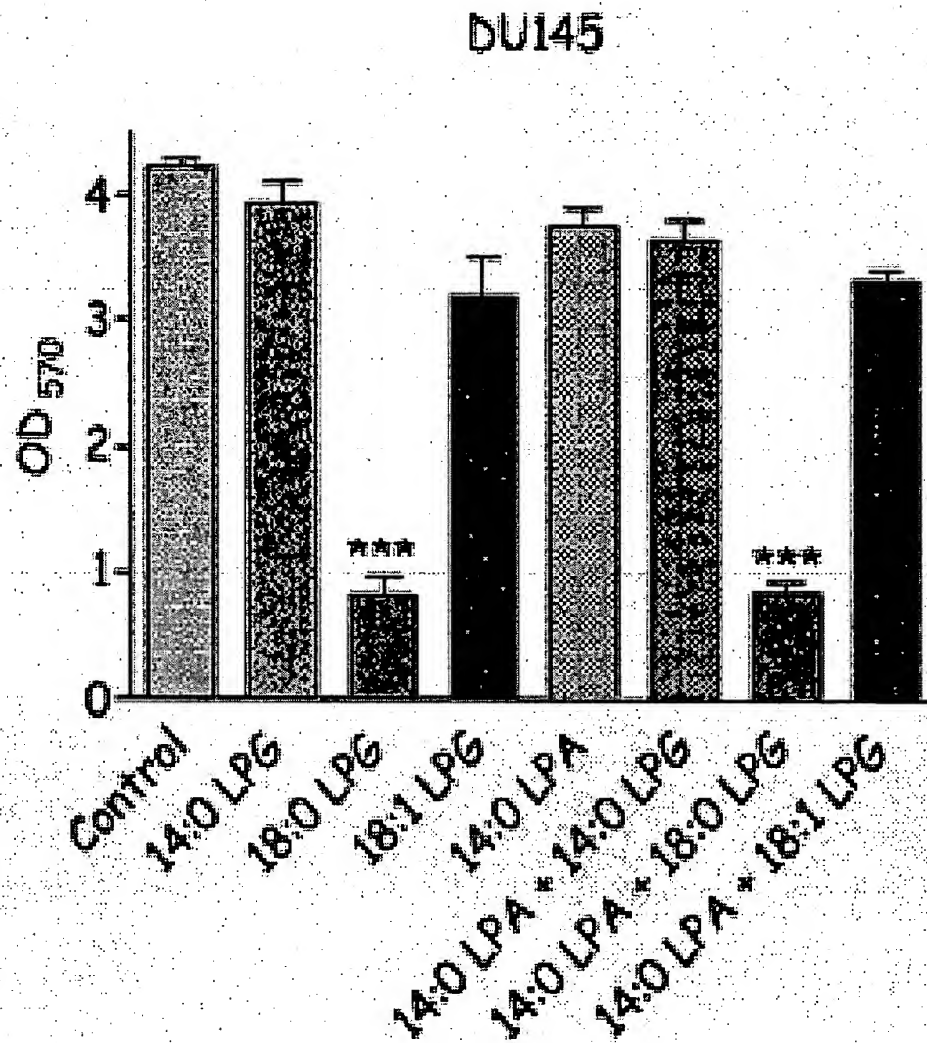


Figure 55

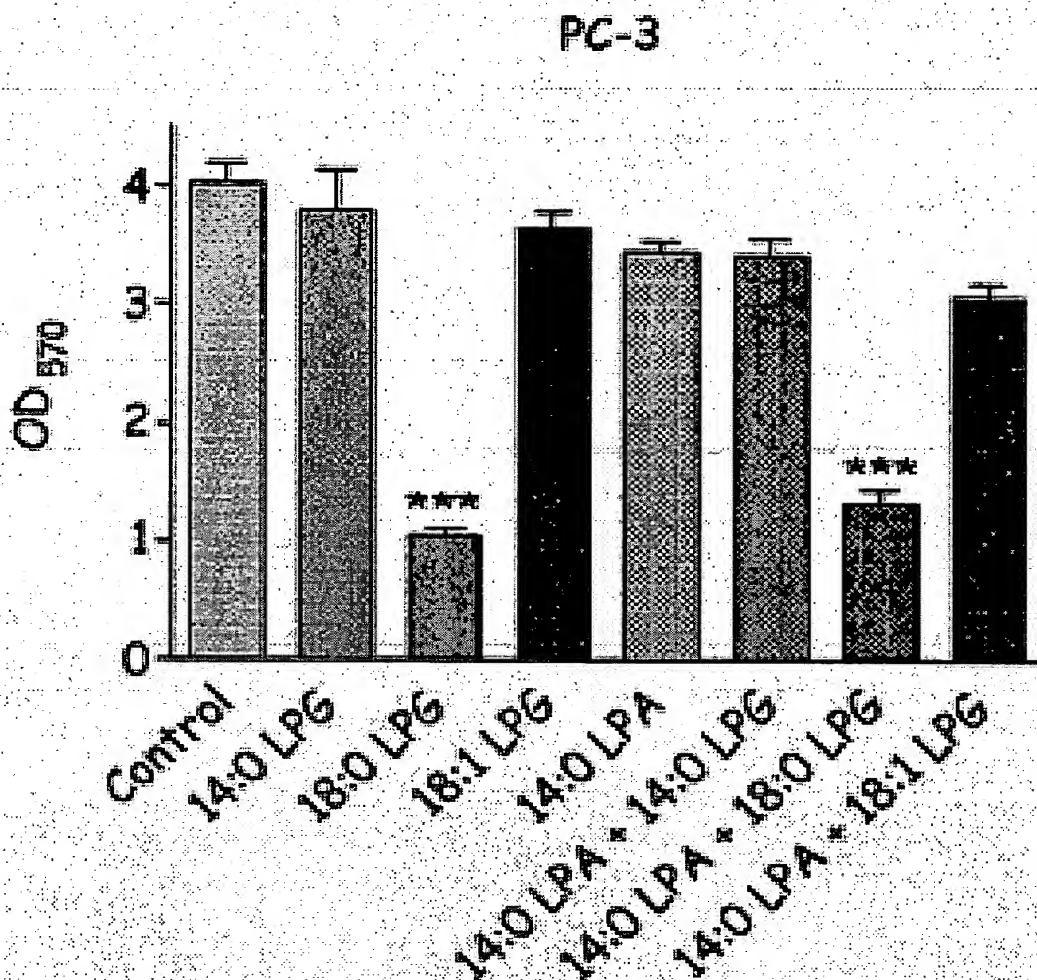


Figure 56